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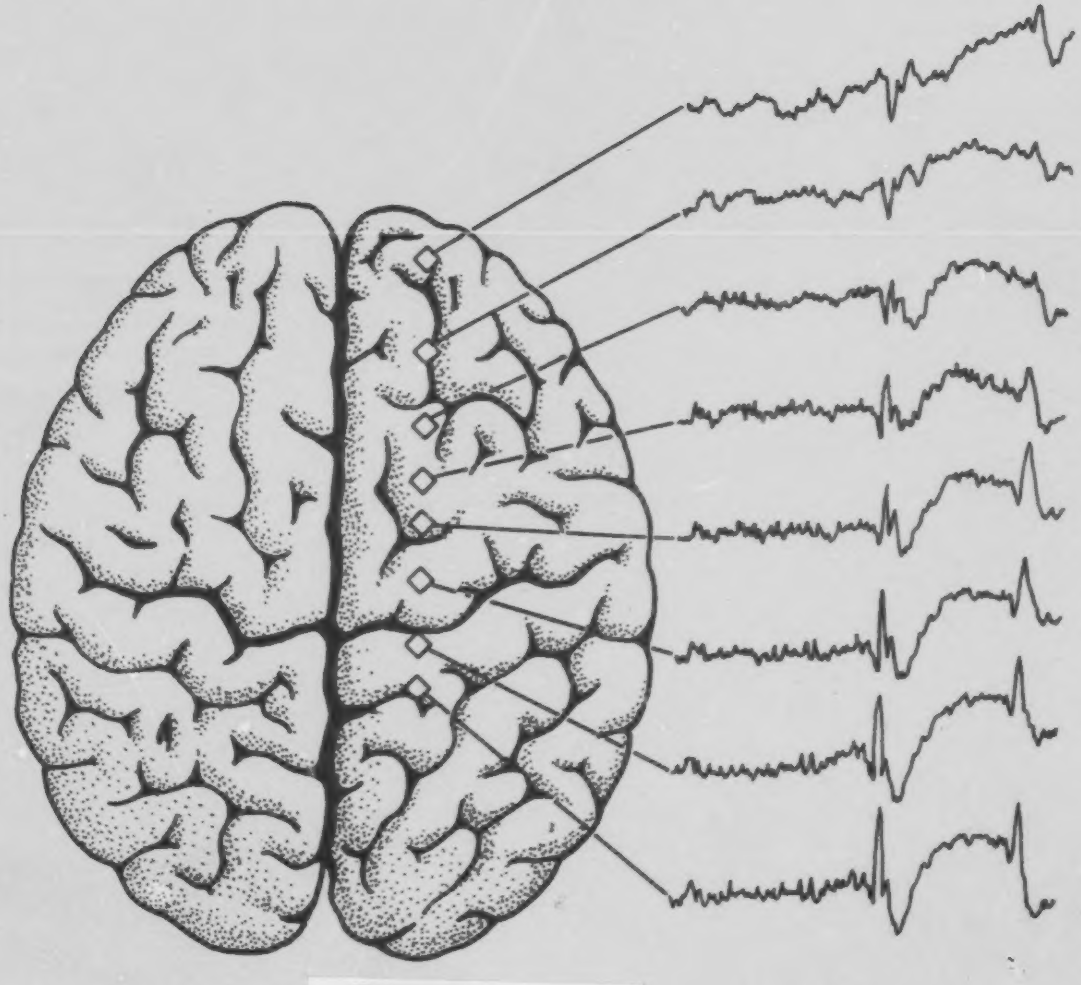

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16. ABSTRACT

This volume is the Proceedings of the Fourth International Congress on Event-Related Potentials of the Brain (EPIC-IV) held in Hendersonville, North Carolina in April 1976. It contains 118 manuscripts including critical reviews and data reports in the following areas of ERP research: 1) electrogenesis and neurochemistry, 2) motor control, 3) information processing, 4) language, 5) developmental disorders, 6) psychopathology, 7) environmental toxicology, 8) scalp distribution, 9) alternatives to signal averaging, and 10) theoretical models. The environmental section assesses the progress of neurobehavioral research on the health effects of environmental toxicants, evaluates the utility of evoked potential research techniques in environmental toxicology, and encourages neurobehavioral research in problems of environmental concern.

Many issues concerning the neurochemical substrate and functional significance of ERPs are discussed with the objective of defining multidisciplinary approaches for resolution. The volume provides useful reviews and models to assimilate the growing body of ERP data from anatomy, physiology, pharmacology, psychology, linguistics, toxicology, neurology, psychiatry, and allied clinical sciences. The proceedings will serve, therefore, as a planning document as well as a progress report in the field of ERP research.

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Hendersonville, North Carolina, April 4-10, 1976

Edited by

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DEDICATION TO WILLIAM GREY WALTER, M.A., Sc.D.
February 19, 1910-May 6, 1977

The Proceedings of the Fourth International Congress on Event-Related Slow Potentials of the Brain (EPIC IV) are dedicated to the memory of William Grey Walter, who died May 6, 1977. He left a world wiser in consequence of his many active and imaginative years as an investigator into the physiology of the mind.

Grey Walter was one of the very early pioneers in the electrical activity of the human brain. Originally a student of Adrian, he joined Professor Golla at the Maudsley Hospital in 1935 to pursue the area of EEG research opened up by Berger and Adrian. His first and very major contribution to EEG was the discovery of delta activity and its localizing value in brain tumor suspects.

Grey Walter was a pioneer who kept moving ahead of the frontiers he himself established. In 1940, he turned his efforts to automatic frequency analysis, "on line," and sought psychological correlates of the changing voltage-frequency profiles. Since single-channel display was frustratingly limiting, he undertook to develop one of the first truly electro-anatomical displays of the brain with his "toposcope" (1952-53). Frequency, voltage, and phase could be derived from 22 electrode points on the scalp. The effects of sensory modulation of the brain were also defined in terms of frequency, voltage, phase, and area.

In 1962, Grey noticed a negative shift that occurred between paired stimuli. His initial interest apparently was in possible modification of sensory evoked potentials during Pavlovian conditioning. With this observation, he opened another frontier, that of the event-related slow potential which he named the Contingent Negative Variation. The work was presented in England and the United States in 1964, and published in *Nature*. While the initial instrumentation that uncovered this phenomenon was crude, further pioneering in computer analysis and display, up to and beyond his retirement in 1975, kept Grey abreast (if not ahead) of the times, and stimulated an increasingly large group of experimentalists to explore the neurophysiology of behavior. Here at last was a key that might fit some of the locks many had been struggling with for years.

These are some of the things Grey Walter has left us; other things are even more important: memories of a probing mind that stimulated others to think, memories of a devoted scientist who would not require that others work harder than himself, and memories of a warm and embracing fellowship upon which all other attributes revolved.

The continued growth of event-related potential research is a tribute to Grey Walter's scientific endeavors, his imagination, and his forceful leadership. The ongoing series of International ERP Congresses is but a small part of his scientific legacy. Grey Walter bequeathed to future generations his inspiration and intellect in the form of extensive and eloquent writings. He was a giant in the field of neurophysiology—a remarkable scientist, author, and personality whose memory will always be cherished by those privileged to know him.

J. R. Knott

PREFACE

This volume is the Proceedings of the Fourth International Congress on Event-Related Slow Potentials of the Brain (EPIC IV) held in Hendersonville, North Carolina on April 4-10, 1976. The volume contains ten sections devoted to the following areas of ERP research: (1) electrogenesis and neurochemistry, (2) motor control, (3) information processing and cognition, (4) language, (5) development and aging, (6) psychopathology, (7) environmental neurotoxicology, (8) scalp distribution, (9) alternatives to signal averaging, and (10) theoretical models. Sections are based on plenary sessions at the Congress and include, in varying form, correspondence summaries, data and review papers, and condensations of discussion.

In memorium.

This series of meetings began with Grey Walter's discovery of the CNV. In failing health, Grey did not attend EPIC IV. As these proceedings were being assembled, we learned with great sadness of his passing. In tribute to the man whose vision and leadership nurtured event-related potential research, this volume is humbly dedicated to William Grey Walter.

Collective planning.

A collective approach to conference planning, pioneered at Bristol in 1973, was used extensively in preparation for EPIC IV. Correspondence panels in the areas listed above were established a year before the meeting to (1) define critical issues, (2) review and synthesize available evidence, and (3) formulate experiments or strategies to resolve issues. Correspondence summaries were precirculated to conference participants and plenary sessions were organized around correspondence panels. Correspondence chairmen served as discussion leaders at EPIC IV and as section editors of the proceedings. This volume is the final product of this lengthy but fruitful experiment in collective planning and communication.

Environmental theme.

Two plenary sessions were devoted to "neurobehavioral indices of environmental insult." The objectives of these sessions were to evaluate the utility of ERP techniques in environmental toxicology and to encourage neurobehavioral research in problems of environmental concern. Neurobehavioral evidence has played a relatively insignificant role in determining current U.S. environmental standards. Reports in this volume from investigators in Austria, Finland, Germany, Italy, and the USSR, on the other hand, indicate that behavioral and evoked potential data play an important role in setting threshold limit values (TLVs) in Eastern and Western Europe. Data presented in the toxicology section and elsewhere in this volume document the sensitivity of ERPs and other neurobehavioral measures to the effects of psychoactive drugs, pesticides, industrial solvents, and other physical insults such as noise and electromagnetic radiations. The evidence argues strongly for increased application of neurobehavioral methods in studying the adverse health effects of environmental toxicants.

Interdisciplinary bridge-building.

Progress in the ERP field depends on the integration of evidence from many disciplines within the neurosciences. ERP investigators include psychologists, psychiatrists, neurologists, and neurosurgeons, although the disciplines of neurophysiology, neuroanatomy, and neurochemistry have not been represented until recently. A major objective of EPIC IV was to recruit investigators from the latter disciplines to begin to bridge fundamental gaps in ERP knowledge. The infusion of new blood and new perspectives produced an exciting concatenation of ideas reflected in the series of tutorial papers and theoretical models which appear in this volume.

Review procedures.

The editing of this volume took far longer than anticipated. Two factors deserve mention. In order to achieve some degree of quality control, all data papers and many review papers were submitted to peer review. Although few papers were rejected, many authors were required to make extensive and repeated revisions. In order to achieve greater clarity and consistency, the editorial staff further revised most manuscripts. The benefits of these efforts, however, must be weighed against the resulting publication lag. I am grateful to the section editors and individual contributors for their cooperation and patience in this frustrating and time-consuming enterprise.

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Supplements.

Dr. Jon Peters prepared an extensive "Bibliography of CNV and Other Slow Potentials of the Brain: Part III" which covers the period between the Bristol Congress (August 1973) and EPIC IV. To facilitate distribution and avoid redundancy with other reference sections in this volume, Dr. Peters' excellent bibliography was published separately in June 1978 as an EPA Research Report (EPA-600/1-78-042). This document is available from the National Technical Information Service, Springfield, Virginia 22161.

A set of manuscripts submitted by several investigators from the USSR who were unable to attend EPIC IV will also be published as a separate EPA Research Report and should be available from NTIS in mid-1979. Further information on these documents may be obtained from D. Otto.

Acknowledgments.

EPIC IV was sponsored jointly by the Biological Sciences Research Center, School of Medicine, University of North Carolina at Chapel Hill and by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. We are deeply indebted to both organizations and their respective directors, Dr. Morris Lipton and Dr. John Knelson, for enthusiastic support and administrative assistance. Funding was provided by EPA Grant R803494-02 to the University of North Carolina. Dr. Lipton was Principal Investigator and Dr. Thomas Wagner was EPA Project Officer.

Many others generously contributed time and talent in organizing EPIC IV and editing this volume. I would especially like to acknowledge the administrative assistance of Bill Heriford and Bobby Wagoner (UNC Extension Division), Jeanne Hernandez (Institute of Environmental Studies), and Elizabeth Clark (BSRC); the technical editorial and graphics support of Bob Kolbinsky, Earnie Caldwell, Webb White, Miriam Harper, Cathy Jo Poole, Pam Barnwell, Mary Woodard, Paul Holder, and Charlie Keadle (EPA General Services Division); clerical support from Barbara Queen and the HERL Word Processing Center, Jo Nichols and the Clinical Studies Division (EPA), Marty Byrd (BSRC), and Pat Reefe; and general assistance from Alex Adams, Gayla and Vernon Benignus, Dick Calvert, Marchell Franklin, Mary Hicks, Debbie Markley, Kim Nguyen, Jim Prah, and Kathy Seiple.

Finally, I would like to express my deep appreciation to W. Cheyne McCallum, Congress President, and John R. Knott, Past President, for their invaluable advice, encouragement, and assistance in all aspects of the organization of the Congress and editing of the Proceedings. The Program Committee also deserves special thanks for strenuous and inspired efforts in organizing correspondence, leading discussion at the Congress, and editing the resultant sections of this volume.

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ABBREVIATIONS

The following standard abbreviations are used in this volume. Other abbreviations are defined in the text when first used. Note that numbers in EP component, stimulus, and international 10-20 electrode designations have not been subscripted in this volume.

AEP	auditory evoked potential
ARAS	ascending reticular activating system
BP	*Bereitschaftspotential* (synonymous with RP)
BPM	beats per minute (heart rate)
COHb	carboxyhemoglobin
CNS	central nervous system
CNV	contingent negative variation
CS	conditional stimulus
d.c.	direct current or, when used in relation to amplifiers, 'directly coupled'
ECoG	electrocorticogram
EDR	electrodermal (skin potential) response
EKG	electrocardiogram (also ECG)
EMG	electromyogram
EOG	electro-oculogram
EP	evoked potential
EPSP	excitatory postsynaptic potential
ERP	event-related potential
FFT	fast Fourier transform
GSR	galvanic skin response
HR	heart rate
Hz	Hertz or cycles per second
IPSP	inhibitory postsynaptic potential
ip	intraperitoneal administration
ISI	interstimulus interval
ITI	intertrial interval
MCV	motor nerve conduction velocity
MP	motor potential
msec	millisecond
MRF	midbrain reticular formation
N1,N2, etc.	first negative peak, second, etc.
P1,P2, etc.	first positive peak, second, etc.
P300	positive wave with peak latency approximately 300 msec after stimulus onset (also P3)
PINV	post imperative negative variation
PMP	premotion positivity
PNS	peripheral nervous system
po	perioral (by mouth) administration
PSP	postsynaptic potential
RCPV	reinforcement contingent positive variation
rms	root mean square
RP	readiness potential (synonymous with BP)
RT	reaction time
S1,S2, etc.	stimulus one, stimulus two, etc.
sc	subcutaneous administration
SCV	sensory nerve conduction velocity
SEP	somatosensory evoked potential
SP	slow potential
SPL	sound pressure level
TC	time constant
TLV	threshold limit value
US	unconditioned stimulus
VEP	visual evoked potential

KEYNOTE ADDRESS

THE SIGNIFICANCE OF NEUROBEHAVIORAL DATA IN SETTING AIR QUALITY STANDARDS

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It is an honor to be invited to take part in this distinguished Congress, and a special honor to be permitted to make some remarks at the opening of the sessions. It was suggested that you might be interested in a very practical topic: the significance of neurobehavioral data in setting air quality standards. Having been involved in some way with such activities for about fifteen years, I shall offer you some observations.

First it must be recognized, that in the United States, neurobehavioral data were significantly used in setting only two community air quality standards–those for carbon monoxide and for lead, and the latter only in the state of California. The carbon monoxide standard was set in California by the Air Resources Board (1970) because the legislature had ordered that air quality standards must be established by a specific date. The only evidence then available on the effects of carbon monoxide in concentrations close to those observed in urban centers were the studies of McFarland's laboratory on the effects on vision (McFarland et al. 1944; Halperin et al. 1947, 1950), Schulte's work (1963) on performance of psychological tests, and work from our laboratory (Beard and Wertheim 1967) on the discrimination of short intervals of time. These all showed effects when 5% or less of the body's hemoglobin had been occupied by carbon monoxide. All the other data then available referred to industrial exposures at much higher levels, with no systematic study of behavioral responses.

It was widely accepted that if the product of the exposure time in hours multiplied by the ambient carbon monoxide concentration in parts per million did not exceed the number 800 there was little probability of any perceptible effect. Applying this formula as a standard would lead to an ambient level of forty-four parts per million, assuming that a stable equilibrium could be reached in eighteen hours. The California standard was established with 15 parts per million averaged over 12 hours, and subsequently changed to 10 parts per million averaged over 8 hours. Later a Federal Primary Air Quality Standard for carbon monoxide (Environmental Protection Agency 1971) was set at 10 mg/m^3 or 9 parts per million, based on very much the same information.

The California lead standard was set about three years ago, based on evidence about the interference of lead with hemoglobin synthesis. Recently, that standard was reconsidered. Reports of impairment in intellectual and behavioral performance of children were at this time taken into account. The stringent standard of 1 1/2 $\mu g/m^3$ was reaffirmed (California Air Resources Board 1975, 1976).

In order to understand the outlook for the use of behavioral data in air quality standard setting, it will be profitable to turn to the standards which have been established in industry for the protection of workers' health. Such standards have been in effect for many decades. There are profound differences between the United States and some other nations in this regard. "In [our country] no serious threat to health is considered to exist as long as the level of exposure does not induce a. . .demonstrable disturbance of a kind and degree that is accepted as an indication of potential sickness; [in the USSR] a potential for ill-health is said to exist as soon as the organism undergoes the first detectable change of any kind from its normal state" (Hatch 1972). Eastern European nations generally follow the Russian pattern, while other nations generally follow the pattern used in the United States, with a great many differences in the interpretation of data. Consequently, international agreements on occupational air quality standards are very few in number and the limits recognized among the nations may differ by a factor of ten. The leading agency for setting such standards for the United States does not recognize that effects demonstrated by evoked potentials are sufficient evidence on which to base standards. On the other hand, Eastern European countries have used such information for many years.

U.S. industrial management, government, and for the most part, labor are comfortable with the kind of standard-setting for occupational health which has become familiar. Efforts to bring new methods which might lead to more stringent controls will be resisted, especially if costly changes in materials, processes, or equipment do not promise immediate tangible benefits for workers. It is not likely to be seen as sound policy to invest heavily in protection from a hypothetical injury which might, if prolonged or oft-repeated, produce only subtle changes in the mental processes of a minority of workers.

Air quality standards for industry are generally based on two major assumptions: (1) that the duration and frequency of exposure can be controlled and (2) that individuals who are unusually susceptible can be detected and transferred to other work. The guidelines for community air quality standards are not so clear and not so generally accepted. Obviously, they must be designed for continuous exposure over many generations. But whom must they protect? It is easy to proclaim that no citizen should be made to suffer the ill-effects of man-made pollution. But does that mean protection for every aged pulmonary cripple, gasping away a life misspent in the consumption of several tons of cigarettes, or the protection of the prematurely born infant not yet ready for independent life?

Some years ago in California, the decision was made to protect *the most susceptible group* of people which could be identified. This has led to consideration of the effects of air pollution on infants, the aged, those with chronic pulmonary disease, and those with cardiovascular disease. It is recognized that it is necessary for people with extreme susceptibility to be protected by the provision of filtered, purified air on an individual basis.

In the face of so much uncertainty about the criteria for air quality standards, what will be the place of neurobehavioral observations? To some degree this will depend on the extent to which they can be correlated with the threat of disease, or with the impairment of practical functions which are recognized as being important. If the alteration of the contingent negative variation can be shown to be a reliable sign of a process which leads to increased risk of automobile accidents, it will carry a great deal of weight. If it is an isolated instance, it is apt to be neglected. The most interesting case is likely to be the one in which the presumed toxicant at a small dose causes enhanced performance on some neurobehavioral task. This phenomenon is well-known to pharmacologists and psychophysiologists, and has been observed in our laboratory with a small dose of ozone in a test of visual perception (Grandstaff and Beard, this volume).

The Environmental Protection Agency as it now stands is not likely to give much attention to neurobehavioral data. In setting a new standard, essential steps are first, publication of the document which reports the criteria on which the new standards will be based—that is, all the relevant data. The drafting of such documents has in the past been done by various groups under contract to the agency. The selection of contractor will influence the content of the draft. At present, only one of the leading figures in the EPA hierarchy has much feeling for neurobehavioral science. The draft, when prepared, will be open to public criticism, but its final form will be decided by a sixteen member advisory committee, which as presently constituted has only one member who has shown an interest in, and an understanding of this kind of work. Finally, the Administrator will act on the advice of his staff and still another advisory committee to promulgate a regulation.

As I read some of the reports prepared for this meeting, several areas for comment emerged. One was the frequency of seemingly discrepant observations and the analysis of those discrepancies. In most instances these could not be resolved because the conditions of experimentation were not the same. There is a need for better controls. That, of course, is what this meeting is all about, and this free and easy exchange of ideas will help to improve the comparability of different studies.

Another thing which emerged is the need for real interdisciplinary cooperation. The first rate psychologist cannot really get useful help from a tyro toxicologist, nor even from a first rate toxicologist, if he keeps him in a purely ancillary role. I am concerned that there is developing an in-group which initiates its new members by making them learn a special language. It is, of course, inevitable that these new ideas require new modes of expression, and that there will be conventional phrases which will be understood by the initiate as symbols for large constellations of ideas. But we must beware of mistaking new complexities of expression for new ideas. Ultimately, our ideas will have value to our fellow men only to the extent that they are understood. The research which is being discussed here this week should be made known much more widely. It should be publicly reported in journals which are seen by a wide range of scientists. It should be reported in a language which can be understood by specialists from other fields.

In the long run, the real contribution of neurobehavioral studies will be deepened understanding of the processes of the nervous system and of the ways they can be affected by external agents. We should not be impatient for practical and applicable results from this very new field of science. It is progressing rapidly as shown by the reports prepared for this meeting. The insights and cumulative data base that derive from meetings such as EPIC IV provide the foundation essential for future applications of neurobehavioral methods to environmental problems including the setting of air quality standards.

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I. ELECTROGENESIS AND NEUROCHEMISTRY

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ELECTROGENESIS OF SLOW POTENTIAL CHANGES IN THE CENTRAL NERVOUS SYSTEM: A SUMMARY OF ISSUES

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Introduction

This summary is based on preconference correspondence concerning the electrogenesis and pharmacological substrate of slow potential changes in the central nervous system. The following individuals contributed to this correspondence:

1. E. Evarts, National Institutes of Mental Health, Bethesda, Maryland.
2. J. Fuster, University of California, Los Angeles, California.
3. B. Libet, University of California, San Francisco, California.
4. T. Marczynski, University of Illinois, Chicago, Illinois.
5. V. Rowland, Western Reserve University, Cleveland, Ohio.
6. J. Skinner, Baylor College of Medicine, Houston, Texas.
7. G. Somjen, Duke University, Durham, North Carolina.
8. J. Stamm, State University of New York, Stony Brook, New York.

Discovery of the contingent negative variation (CNV) by Grey Walter and his colleagues (1964) and Bereitschaftspotential (BP) by Kornhuber and Deeke (1965) gave significant impetus to the recent study of SP changes in relation to overt behavior. These findings were paralleled by discovery of a slow positive potential (the P300 wave) and related components that reflect cognitive events (Sutton et al. 1965). The basic approach to this work may be characterized as "electrophrenerrianology" (EPology)–that is, the study of the localization of psychological processes in the brain through analysis of electrical "bumps" on the human skull, with the Skinnerian assumption that the determination of the variables that influence those "overt" events is sufficient to their explanation. The assumptions inherent in this approach may lead to fallacious conclusions in relation to human perception and subjective sensory experiences unless there is rigorous validation of subjective experience and knowledge of the physiological bases of the potentials. Whereas the psychological aspects of such work are usually well controlled and operationally defined, the neglect of intracerebral neurophysiology is evidenced by the lack of a single investigation of cortical neuronal firing patterns associated with the CNV, and only one relating the BP to single neuron activity (Gantchev 1974). Furthermore, very little discussion at three previous ERP Congresses was devoted to recordings in animals, and among those papers (Borda 1970, Donchin et al. 1971, Hablitz 1973, McSherry 1971, Rebert 1972), only McSherry directed attention to causal mechanisms.

Yet knowledge of the causal mechanisms of the CNV and other event-related phenomena is critical to their full understanding and to their proper interpretation in relation to behavior and covert psychological processes. It is possible, for example, to record an identical scalp potential under a variety of intracerebral conditions–that is, when the specific neuronal/glia elements involved differ (e.g., generation of a surface-negative potential by dendritic depolarization in contrast to somatic hyperpolarization). Whereas the surface potential in the two conditions could be the same, the physiological consequence would be opposite. Such details must be known to adequately relate scalp potentials to molar events.

There has, of course, been a long history of interest in SP phenomena of the brain aside from the CNV, BP, and P300–indeed, from the very inception

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of cerebral electrophysiology (Caton 1875). Because Caton used slow recording galvanometers that integrated oscillatory potentials, he could not clearly distinguish real SPs from rhythmic after potentials. Modern entry into this field was initiated by Gerard and Libet (1940) who were able to clearly distinguish SPs from oscillatory activity. Their work laid the early foundation for delineating mechanisms of SP genesis and it continues to this day (Libet, this volume). From that somewhat independent stream of research, a body of evidence has accumulated that is relevant to studies of the CNV. The specific neurophysiological and neurochemical mechanisms elaborated by Libet and his colleagues in the sympathetic ganglion provide useful models for the study of CNV genesis centrally. Another general stream of research that can shed light on the mechanisms of event-related SPs are studies of intracerebral neurophysiology undertaken in behavioral contexts similar to those used in the study of SPs (Fuster 1973). Given comparable situations, interexperimental similarities between SPs and neuronal responses can be evaluated. There are also several investigations involving direct comparisons of SP and unit responses (Fromm and Bond 1964, 1967; Rowland 1974; Rebert 1969, 1973b), but few involving the behaving organism.

Because it is increasingly obvious that EPology is not an adequate approach to the full understanding of event-related SP phenomena, consideration of electrogenesis has been included as part of this fourth congress on event-related SPs. The primary objective of this review is to delineate important issues with regard to mechanisms of SP genesis in order to facilitate their early resolution. Investigators from neurophysiology (Evarts, Fuster, Skinner), neuropharmacology (Libet, Marczynski, Somjen), and physiological psychology (Rebert, Rowland, Stamm) engaged in a correspondence to develop a multidiciplinary view of the problem of SP genesis with the following objectives:

1. Delineate critical issues concerning SP genesis, the unknowns at this point in time.
2. Describe the state of the data to determine what needs to be done experimentally, theoretically, and technically to resolve critical issues.
3. Determine in a broad sense where SP electrogenesis research is headed: What trends are occurring, and whether the research is leading to any general principles of brain function.

Three general categories of critical issues were raised:

1. *Typology of SPs*–Several types of SPs can be identified and defined from different frames of reference. From a phenomenological view, SPs have been defined as "motor readiness" events, "expectancy waves," and "postreinforcement potentials." In contrast, SPs have also been defined in terms of their temporal characteristics, for example, "phasic" (CNV-like) versus "tonic" long-lasting (postreinforcement) SPs.
2. *Experimental Issues*–These issues include specific questions such as the relationship of SPs to neuronal activity, the neurochemical mediators of SPs, and the role of potassium and glia in SP genesis.
3. *Technical Issues*–These issues relate to technical limitations that preclude or impede advances and interpretations in specific research strategies.

These issues are reviewed below.

Review of issues

Typology of SPs

Several ways of categorizing or defining SPs are discussed here. This list is probably not exhaustive, and the categories are not mutually exclusive. SPs can probably be best differentiated on the basis of multiple categories.

Temporal classification: There are relatively constant potentials between almost any two regions of the brain or between the brain and extracerebral sites. The potential of the mammalian cortical surface is approximately 15 mV positive with respect to cortical layers V-VI (Aladjalova 1964), and the surface is 1 to 3 mV negative with respect to frontal bone (Fromm and Bond 1964). These potentials, while relatively constant, may fluctuate with very long periods (Aladjalova 1964) or with the sleep-wakefulness cycle (Caspers 1963; Wurtz 1965a,b). The "resting" potential exists in contrast to "reactive" SPs that are of relatively short duration (1 to 20 sec) and that are usually evoked by transient sensory or psychological events (e.g., CNV). SPs may, then, be either oscillatory or nonoscillatory, and the latter can be further subdivided on the basis of their duration into two general classes–(1) tonic (resting) potentials with durations of minutes or hours and (2) phasic (reactive) potentials with durations of seconds. This latter dichotomy might also parallel SP types that do and do not correlate with massed unit activity (Sheafor and Rowland 1974) and phasic CNV-like SPs observed in many parts of the monkey's brain, in contrast to cumulative postreinforcement potentials observed only in the cortex (Steinmetz and Rebert 1973).

Functional classification: The functional significance of SPs may be considered at two different levels, i.e., with respect to neuronal activity or molar behavioral/psychological events. Negative and positive postsynaptic potentials (PSPs) measured at the outer neuronal membrane surface with microelectrodes are associated with excitation and inhibition of the neurons, respectively, but the relationship of slow field potentials (measured with macroelectrodes) to neuronal firing is not clear. Given clarification of that relationship, SPs might be defined in terms of their excitatory or inhibitory consequences.

A variety of factors related to sensory input, behavior, and covert psychological processes may elicit SPs, which can be differentiated into (1) those elicited unconditionally by external events such as sensory stimulation and reinforcement; and (2) those elicited conditionally during situations like the cued RT task. Other classes of SPs include those related (1) to "spontaneous" alterations of arousal, attention, and sleep-wakefulness; and (2) endogenous or induced tissue abnormality such as the SPs preceding seizures or accompanying cortical spreading depression or surgical injury (Irwin et al. 1975).

Other functional classifications have been suggested based on phenomenological interpretations of the most salient psychological process presumed to be represented by the SP. For example, the CNV has been related to cognition, expectancy, motivation, waiting, and attention. Until the functional significance of SPs is unequivocally established, such presumptive labels should be avoided.

Mechanistic classification: Three general classes of SPs are delineated here based on (1) neuroanatomical arrangements, (2) membrane and neurochemical mechanisms in neurons, and (3) extraneuronal mechanisms.

SPs may be classified with respect to both particular and general neuronal arrangements. The organization of neurons varies from locale to locale in the brain. Some regions like the cerebral cortex, hippocampus, and cerebellar cortex are characterized by systematically oriented neurons that develop electric dipoles directly related to the physical organization. In contrast, regions like the reticular formation and caudate nucleus do not have such well-defined neural arrangements, yet they also exhibit SP responses (Rebert 1972). The SPs generated in these two types of tissue might be referred to as "dipole" and "reticular" types. A difficult question is to determine the mechanisms of SP genesis in the latter type of tissue. Since the neurons are not systematically oriented, the net field produced by neuronal membranes might be zero, the separate fields cancelling one another. But, as Libet asked, if a field-recorded SP is generated by a type of glial cell, would there not have to be a sufficient gradient in SP somewhere along the cell axis to develop the external field? What is the evidence for such axial gradients in glial cells? In addition, would it not be necessary for glial processes to have some systematic arrangement to preclude cancelling of their fields? What alternatives can be suggested? Somjen (this volume) provides a model of how glia might be involved in SP genesis.

The general intracerebral system involved in the production of surface potentials may also differentiate apparently equivalent surface potentials. This is reflected by data of Skinner and Yingling (1976) showing that frontocortical SPs evoked by either a novel stimulus or a neutral reinforced stimulus appear to be the same in that the identical physical stimulus evokes them and their anatomical distributions are the same. However, the subcortical correlates of those two seemingly identical SP events are different. The response in *n. reticularis thalami* to a novel stimulus does not require the integrity of the inferior thalamic peduncle (a bidirectional pathway interconnecting the medial thalamus and frontal cortex), whereas the conditioned response recorded in this structure does require intact connections with the frontal cortex. Thus, knowledge of the subcortical correlates of the frontal potentials separates them into distinct SP events, even though the actual local response parameters are the same and are presumably mediated by the same local generators. The latter presumption requires further examination because different local neural aggregates could be generating morphologically similar waveforms.

Many neurons are "mosiac" in the sense of being sensitive to a variety of transmitter substances. In addition, the effect of synaptic events depends upon the influence of nontransmitter chemicals that are both endogenous and exogenous to neurons. Chemical "modulators" are endogenous substances that function in a homeostatic way to regulate the rate of depolarization or hyperpolarization initiated by a synaptic transmitter. Similarly, blood-borne substances exogenous to neurons can facilitate (mediator) or attenuate (moderator) the rate of synaptic transmission or axonal conduction, or act to alter transmitter release or change the action of a modulator (Myers 1974). As indicated by Libet (this volume), slow SPs are associated with such actions and can be classified on the basis of their neurochemical substrate.

A variety of extraneuronal factors are also known to produce SPs. They include potentials generated by glial membranes, vascular flow, differential pH, CO_2, blood-brain barrier, and perhaps others.

Tonic and phasic SPs constitute two major classes that can be differentiated on a number of definitional factors. Tonic SPs are contrasted with phasic ones, by definition, in terms of temporal characteristics. In addition, phasic SPs appear to be closely related to transmitter release, neuronal organization (dipoles), and waking psychological/behavioral events, while tonic SPs appear to vary with metabolic factors, injury, and the blood-brain barrier. Tonic SPs may not differ from one intracerebral locale to another, may not relate to neuronal organization, and are, perhaps, associated with modulator and moderator/mediator actions on neurons.

We are left with the general question as to the best way(s) of classifying SPs. Somjen emphasized the need to avoid the kind of confusion that has arisen around the term alpha rhythm, customarily distinguished from EEG spindles, except by Andersen and Andersson (1968) who regard the two as identical because of a suspected common generating mechanism. He suggests that SP categorization should be based either on phenomenology or electrogenesis, but not on both, although, as suggested above, a multidimensional scheme may be most appropriate.

Experimental issues

Specific experimental issues related to electrogenesis may be summarized in terms of seven major considerations:

1. Spatial distribution of SPs in the central nervous system (CNS).
2. Neurochemical factors related to SP genesis.
3. Relations between neural activity/excitability and SPs.
4. The role of potassium and glia and other "nonresponsive" cells in SP genesis.
5. Intracerebral relationships inferred from SP responses.
6. The interaction of SP types.
7. The general question of how knowledge of SP electrogenesis might improve understanding of the behavioral/psychological relevance of SPs.

Spatial distribution: Given the variety of factors that contribute to SP genesis, it is likely that SPs can be recorded from any region of the CNS under one condition or another. The distinction between resting and reactive SPs is important in this context, as resting SPs—like those associated with the sleep-wakefulness cycle—may appear with similar polarity and time course throughout the brain (Wurtz 1966), whereas reactive SPs, e.g., those elicited in the cued RT task, exhibit different polarities, waveforms and amplitudes in different regions of the brain (Rebert 1972, McCallum et al. 1973). The question of distribution in the brain is, therefore, most pertinent to the latter type of SP. Event-related phasic SPs have been observed in several nuclei of the thalamus, hypothalamus, basal ganglia, nonspecific reticular nuclei, and limbic structures (amygdala, spetum, cingulate gyrus) as well as over a large extent of the cortical surface (Haider et al. 1968, Irwin and Rebert 1970, Rebert and Irwin 1969, McCallum et al. 1973, Rebert 1972; Hayward et al. 1966, Vastola 1955, Rowland 1968; Donchin et al. 1971, Borda 1970, Hablitz 1973). The significance of the scalp distribution of SPs in humans is the subject of a separate section in this volume.

Neurochemistry: Two related questions can be asked with respect to the actions of chemicals in the genesis of SPs. First, which chemicals acting on neurons or glia cells produce or modify slow membrane potential changes? Second, can SP responses in particular regions of the brain be related t internuclear pathways defined by their neurochemical properties? Some evidence is available with respect to the first question (see Marczynski and Libet, this volume). On logical grounds, the second can probably be answered in the affirmative, although direct evidence is lacking. It is probably true, for example, that positive SPs in the caudate nucleus depend to some extent on the dopamine pathway that originates in the ***substantia nigra***.

There is some question concerning the role of transmitter substances in SP genesis since, as Marczynski (this volume) points out, the term implies a brisk and quickly reversible effect on neurons. The release of acetylcholine (ACh) in the cortex in association with surface SPs accompanying wakefulness suggests a possible transmitter role in SP production. On the other hand, ACh has muscarinic and nicotinic actions, the former perhaps not representing a typical (brisk) transmitter phenomenon, but a modulator action (Libet, this volume). An additional confounding observation is that ACh may also affect glial membranes, producing slow, long-lasting depolarization. Whether this is a direct effect on glia or a secondary consequence of potassium released from muscarinically activated neurons is not certain. This consideration is important since the sensitivity of glial cells to ACh could, theoretically, result in large SPs without any obvious correlation with neuronal activity as observed by Sheafor and Rowland (1974). Marczynski marshals evidence from a variety of sources suggesting that cortical surface negative SPs are mediated by cholinergic mechanisms. Since the cholinergic component of the ascending reticular activating system (ARAS) exerts a strong facilitating effect on thalamic relay neurons, there is reason to conjecture that thalamic SPs observed by McCallum et al. (1973) and Rebert (1972) may also be cholinergically mediated.

Paradoxically, antimuscarinic drugs such as atropine and scopolamine, known to block negative SPs and the desynchronization induced by ARAS stimulation, in the same dose range also block the occurrence of alpha-type synchronization in men and cats (post-reinforcement synchronization of 7 to 9 c/sec) associated with epicortical positive SPs (reward contingent positive variation or RCPV). Does this mean there are pharmacologically identical but functionally different, and even opposed, cholinergic mechanisms? After systemic administration of scopolamine, the dc potential of the cat's cortex (posterior marginal gyri) remains stable, i.e., the SPs show little fluctuation despite maintenance of bar pressing performance. Furthermore, subsequent administration of physostigmine to increase the tone of the cholinergic systems restores both the negative SPs during unrewarded bar presses and the [illegible] during consumption (Marczynski 1971 and [illegible]).

Dopaminergic and cholinergic influences in the production of slow excitatory and inhibitory postsynaptic slow potentials (s-EPSPs and s-IPSPs) are reviewed by Libet (this volume). Sympathetic ganglion cells are capable of responding to orthodromic (preganglionic) volleys with a slow IPSP and a slow EPSP, the s-IPSP in response to the transmitter dopamine and the s-EPSP in response to acetylcholine, acting muscarinically (Libet 1970). Both slow PSPs have synaptic delays in the tens and hundreds of msecs and durations of many seconds. Both are generated without any detectable change in membrane resistance by electrogenic mechanisms that may depend on active ion transport. Generation of these prolonged responses without the necessity of ionic leakage, in contrast to that of the "classical" or "fast" PSPs, allows their achievement without the excessive energy requirements for restoration of ionic concentrations. If such monosynaptic s-PSPs provide possible models for some neuronally generated SPs, it would be profitable to study their incidence in the CNS in relation to SP responses.

An additional function of dopamine consists of a true modulating action on neuronal reactivity to ACh (Libet and Tosaka 1969, 1970; Libet et al. 1975). Brief exposure to dopamine enhances slow muscarinic response to ACh (s-EPSP responses) up to several hours or longer. This modulatory function has important implications for behavioral, motivational, and memory processes. It could provide a basis for long-lasting alterations in SP responses, especially when such alterations are concomitants of behavioral modifications.

The neurochemistry of the CNV is an issue of specific concern. Thompson et al. (this volume) provide preliminary evidence and a brief review of pharmacological effects on the CNV in man.

Relation of SPs to neural excitability: Slow potentials at the cortical surface may reflect a variety of events occurring in cortical neurons, including somatic and dendritic depolarization or hyperpolarization in any combination. Thus, surface SPs could occur in the absence of neuronal firing, reflecting only a change in the dynamic equilibrium of dendritic depolarization and somatic hyperpolarization, perhaps resulting in a more reactive state (McSherry and Borda 1973). In contrast, extracellular slow field potential changes may accompany changes in the average firing rate of neurons. Study of these two questions requires substantially different experimental approaches. The first necessity is to determine the relationship between SP responses and neuronal firing, and in the absence of changes in firing, to determine if SP responses reflect changes in neuron thresholds.

There are two types of evidence available for assessing the relationships of SP and neuronal activity: (1) indirect, inferential data based on interexperimental comparisons and (2) direct correlation of units and SPs. Indirect evidence regarding cortical SPs comes from SP and unit behavior observed by different experimenters using similar experimental paradigms. Fuster (1973), Fuster and Alexander (1971), Stamm (1964), and Stamm and Rosen (1972) have studied units and SPs in monkeys performing delayed response tasks. The results suggest that surface-negative SPs are associated, in some portions of the delay period, with increased neuronal discharge. Another comparison can be made between studies of premotion behavior of cortical units (Evarts 1966, 1973) and studies of slow readiness potentials (Kornhuber and Deeke 1965). The occurrence of increased cellular firing in the cortex in association with surface-negative SPs implies that SPs are due, at least in part, to dendritic depolarization, since a preponderance of somatic depolarization would be reflected by a surface positive SP.

Data from direct comparisons of SPs and single units in immobile preparations are inconsistent (Li and Salmoiraghi 1963) and has rarely been obtained in behavioral contexts. However, Gantchev (1974) concurrently recorded single unit activity and readiness potentials in monkeys and found a preponderance of units increasing firing during surface-negativity, with a mixture of no responding and decreased cortical cell firing in association with surface-positive SPs. Marczynski (this volume) found surface-negative components of postreinforcement synchronization in phase with cortical cell firing. A small sample study of ten neurons suggested that marked reduction of firing accompanied postreinforcement positive SPs. Yingling and Skinner (1975) and Skinner and Yingling (1976) observed that single units in *n. reticularis thalami* increased firing in association with negative SPs and decreased firing with positive shifts.

Measurements of massed unit (MU) activity in the cortex and subcortical regions give similar results. Rebert (1969, 1973b) showed that negative and positive SPs evoked by light flash in the lateral geniculate accompanied increased and decreased MU activity, respectively. Sheaffor and Rowland (1974) found that reactive cortical surface-negative SPs accompanied increased cellular discharge. This result was complicated by additional findings that long-duration "expectancy" SPs were not associated with systematic changes in MU activity. The technical consideration of the sensitivity of MU measures to small unit discharge was raised. It appears that, despite differences in neuronal morphology and specific generating mechanisms, the polarity of surface SPs and those in subcortical regions reflect the state of neuron activity in a similar way, i.e., negativity is associated with increased firing. However, either relationship is possible and at this time the determination of SP/unit relations requires substantiation in each case. Ultimately, repeated demonstration of the same relationship in a variety of experimental settings and nuclei might allow a firm generalization about SP polarity and unit firing to be made.

Role of "nonresponsive" cells and potassium in SP genesis: Neural membrane shifts may occur via regulation of the extracellular ionic concentration of K^+, a mechanism that Ranson and Goldring (1973a, b,c) have linked with glial cell transactions. The electrogenesis of extracellular SPs could derive, in part, from glial membrane shifts, or SP generators could be associated with other biophysical processes of neurons and glia that have not as yet been explored. Rosenthal and Somjen (1973), for example, showed a correlation between cellular metabolic activities and local SP shifts. Metabolic end products could, in turn, affect cerebrovascular flow, a phenomenon that has also been associated with SP shifts (Woody et al. 1970). Somjen emphasizes the importance of recognizing the source of potassium when it accumulates in extracellular fluid. Sources include terminal axon arborizations; cell bodies, dendrites, and axons of spiking neurons; cell bodies and dentrites exhibiting nonspike synaptic currents; and small (short axon) cells. Determination of the precise source is difficult due to the complicated architecture of tissue.

The role of neuroglia as a generator source of sustained potential shifts is extensively reviewed by Somjen (this volume). He suggests that the theory of glial generation is compatible with the theory of cholinergic mediation of event-related SPs (Marczynski, this volume). It is conceivable that, in normal cortex under physiologic conditions, the most abundant sources of potassium are activated by cholinergic input. The idea of direct ACh action on the glial cell membrane is less attractive because it implies the extrasynaptic diffusion of ACh.

Whereas glia have received considerable attention as possible SP sources, Rowland points out that not all "silent" cells of the cortex are glia. He suggests that attention be directed to a possible role of such cells in the production of SPs. Skinner suggests too that calcium has not been adequately studied in terms of its role in the production of SPs.

Intracerebral relations: In the cued RT task, SP polarity appears to differentiate mesencephalic and thalamic nonspecific arousal mechanisms from basal ganglia/limbic structures. The former exhibit negative and the latter exhibit positive SPs (Rebert 1972). It has been suggested (Rebert 1977) that these SP parameters reflect a reciprocal interactive state between the two arousal systems described by Routtenberg (1968).

Observing SP changes in one region of the brain in response to manipulations of other regions appears to be a useful method of studying intracerebral relationships (O'Leary and Goldring 1964, Arduini 1958, Skinner and Yingling 1976). However, caution needs to be exercised in generalizing from experimentally derived relationships under one set of conditions to relationships in other circumstances. For example, evidence suggests that activity in mesencephalic reticular regions has a primary role in the production of surface-negative SPs (Arduini 1958), but trial-by-trial analyses of SPs in nonspecific nuclei and on the cortical surface in the cued RT task indicate that the two regions were not coupled in terms of SP covariation (Rebert 1977). In contrast, the latter analyses suggested that the caudate nucleus and amygdala were coupled during the foreperiod of RT. Therefore, one cannot conclude from the demonstration of anatomical connections and functional interaction between nuclei in one situation that the nuclei are functionally coupled in other situations.

The foregoing indicates the necessity for determining intracerebral dynamics related to particular behavioral/psychological states. Analysis of SP fluctuations appears to be one way to achieve this objective. Skinner's work (this volume) combining SP measures and selective intracerebral blocking has also been fruitful in defining functional paths related to specific behaviors. He suggests an important role of thalamocortical projections, especially the inferior thalamic peduncle, in frontal SP genesis. In contrast, Zappoli et al. (this volume) argue that CNVs in humans occur despite extensive prefrontal isolation and disruption of thalamocortical projections. It has been alternatively suggested that the ventral motor thalamus is involved in CNV genesis (Haider et al. 1968). Also since the caudate nucleus exerts an inhibitory influence on the cortex, reflected in surface positive SPs (Buchwald et al. 1967), and positive SPs occur in the caudate in association with cortical CNVs (Rebert 1972, McCallum et al. 1973), it is conceivable that the CNV could be due, in part, to release from caudate inhibition. In addition, Fuster (this volume) has proposed that prefrontal unit activity, and correlatively SPs, are modulated in part by a visual transcortical pathway involving inferotemporal-prefrontal connections. These findings represent the humble beginning of an understanding of how different brain regions interact to generate SP responses. These results also indicate the usefulness of employing SP responses to assess intracerebral relationships.

Interaction of SP types: The determination of how different SP types interact is an essentially untapped area of inquiry. Some specific questions and possible ways of studying interactions include the following. How might slow glial membrane depolarizations affect neural membranes? Could glial cells regulate the neural equilibrium potential of K^+ and, therefore, the membrane resting potential? Can glia be selectively blocked (e.g., by application of morphine to the cortical surface–Roitbak 1969) to determine their contribution to SPs?

Tonic and phasic SPs and their interaction can be observed concurrently in some behavioral contexts. Rebert et al. (1976) observed dc level changes on the human scalp preceding CNV trials in association with forearm muscle tension induced by having subjects lift weights with a hand grip. There was a direct relationship between the amount of weight pulled and the tonic dc level up to a point (30 lb), after which additional tension produced no further SP shift. However, CNV amplitude showed no increment between 0 and 15 lb, but increased 5μV between 15 and 30 lb. It remained at the larger value at 45 lb. While the pretrial tonic dc shift reached asymptote at 30 lb, an enhanced CNV was superimposed on it, suggesting that the two potentials were independently generated. Similarly, in monkeys there was no apparent interaction between CNVs and a tonic postingestion frontal negativity observed by Steinmetz and Rebert (1973). However, when the cortical dc level shifted several mV negative for an unknown reason in one instance, CNVs were absent. These findings are relevant to the hypothesis that CNV reduction under stress in highly anxious subjects is due to the presence of a physiological ceiling for SP genesis (Knott and Irwin 1968, 1973). Although a ceiling appeared to be produced by muscle tension (which is perhaps analogous to excessive arousal produced by anxiety), CNVs were still apparent. Thus the data did not support the type of interaction between tonic and phasic SPs predicted by the ceiling hypothesis. The monkey data were partially supportive, but only in the context of extremely large background shifts, which should be readily detected on the human scalp. Pirch (this section) presents further evidence concerning the relationship of tonic and phasic negative shifts in rats, suggesting that the ceiling hypothesis is valid.

Relevance of SP genesis to behavioral interpretations: All the issues discussed above are pertinent to the attempt to relate SP phenomena to behavioral/psychological processes. The location of SP phenomena in the brain provides information about particular nuclei and general systems involved in specific behaviors, while SP changes produced by anatomical and neurochemical manipulations can reveal functional pathways that couple nuclei. SP and unit recordings may reveal excitatory and inhibitory patterns in general intracerebral systems that mediate particular behaviors. The delineation of ionic mechanisms in SP genesis would provide additional detailed information about brain-behavior relationships. With respect to SPs, however, efforts to define systems are at a primitive level. With few exceptions (Skinner, this volume), SP measures are not currently being used as a tool to delineate general cerebral systems related to the cued RT task or conditioning paradigms or to specify dynamic intracerebral interactions. In other contexts, however, this kind of systems approach is making significant strides (John et al. 1973).

It is worth reiterating that a given behavioral/psychological state is a dynamic affair in terms of configurations of brain states, and that the behavioral significance of a given electrophysiological event such as the CNV, no doubt, depends upon the simultaneous state of SPs (and other events) in many brain regions. The dynamic and multivariate nature of brain activity is, perhaps, related to the difficulty in predicting even simple behaviors from physiological events like the CNV. Reaction time, for example, correlates weakly with a wide variety of biological indicators (heart rate deceleration, CNV amplitude, alpha abundance, alpha phase, alpha asymmetry, muscle tension). It would seem useful to apply multivariate techniques (cf. Donchin, this volume) to determine what combination of biological indicators taken together best accounts for RT variability. In this case, SP responses recorded from an array of intracerebral electrodes would contribute substantially to our understanding of the general psychophysiological system that underlies reaction time behavior.

Technical issues

Rowland raised the question whether MU recordings are sensitive enough to reflect small unit changes associated with SPs. This is important for interpreting apparent dissociations between SP and unit activity. He also raised the issue of SPs being confounded with impedance shifts. Study of the relationship of this parameter to other electrical events is badly needed.

Another question of interest is the adequacy of sytemic administration of pharmacological agents in the study of SPs. For example, if a shift is produced or altered following a systemic dose of atropine to block cholinergic synapses, what can be concluded? The nucleus in which recordings are being made might be reacting to a local change in adrenergic synapses consequent to cholinergic alteration of a nucleus which sends efferents to the recorded area. For example, cholinoceptive cells in *pars compacta* of the *substantia nigra* project dopaminergic fibers to the caudate nucleus. Systemic administration of an anticholinergic agent could block the *nigra* and indirectly cause a change in the caudate, a change that would, in all likelihood, be erroneously attributed to direct cholinergic mediation in the caudate. Thus, the use of intracerebral perfusion of neurochemicals (Myers 1974) in conjunction with electrophysiological recordings is another valuable combination too little used in SP research.

The growth of glia around electrode tips seems to impair the quality of dc recordings (Skinner, personal communication), and electrode impedance changes also appear to do odd things to Emde on-line calibrators. In the absence of changes in event-related potentials, on-line calibration signals have been observed to either slowly appear or disappear over several weeks of recording from a particular electrode in a particular monkey, while not changing in other monkeys (Rebert, unpublished observations).

Libet expressed the need for improved intracellular recording techniques that would permit rapid impaling of cells combined with the capability to hold the cell for long periods without significant leakage across the membrane. Without better techniques, the critical questions of neuronal PSPs and excitability in relation to various SPs and behavioral functions will probably remain unresolved. A recent development of a "sharpened" glass micropipette by Brown and Flaming (1975) offers some hope along this line. Chronic implantation of subdural and subcortical nonpolarizing dc recording electrodes, which are not toxic to neural and glial tissues, is also necessary for the longitudinal study of behavior in relation to SPs. Rowland (1961) and Rebert and Irwin (1973) have described the construction of nonpolarizing electrodes suitable for this purpose.

Libet expressed the need for geometric models of different types of neural and glial configurations from which slow potential parameters can be predicted. Volume conduction models have been proposed for auditory (Vaughan and Ritter 1970), visual (Vaughan 1974), and somatosensory EP components (Goff et al., this volume). Models relating field potentials to neural architecture have been worked out in greater detail for the olfactory bulb (Rall and Shepherd 1968; Freeman 1975, 1976).

Conclusions

This summary has only partially addressed the goals set forth in the introduction. The ultimate objectives of this area of research have not been clearly defined nor have the practical applications been adequately examined, although there are certainly pursuits in the applied direction, e.g., studies related to epileptogenic mechanisms (Prince et al. 1973). A pertinent question here is the extent to which obtaining "molecular" information about SPs—especially the CNV, which may have diagnostic uses—increases the power of their medical application. Would the CNV be more useful if its exact electrogenesis and pharmacological genesis were known? Perhaps, then, abnormalities in various CNV parameters would indicate specific intracerebral abnormalities. In this same vein, changes in the dynamic intracerebral patterns of SP responses might be sensitive indicators of brain alteration by low levels of environmental toxicants; and, if so, knowing the mechanisms of SP genesis might help to pinpoint the mechanisms of action of toxic agents. An exciting possibility for future application is presented by Stamm et al. (this volume), who suggest that biofeedback procedures that alter frontal SP levels influence the rate at which learning occurs. Some critical issues have been delineated in this summary and several points of direct experimental attack have been suggested. A summary of the general state of knowledge concerning SP genesis has been provided, and an indication of trends in research has been included implicitly.

It is apparent that the electrophrenerrian approach to the study of SP and behavioral relationships is inadequate. Elaboration of SP electrogenesis is necessary and demands interdisciplinary cooperation as much as any other specialized area in neuroscience. Because SPs are sensitive indicators of endogenous and exogenous influences on the brain, the experimental psychologist in league with the electrophysiologist possesses a powerful tool for studying brain-behavior relationships. Such studies have ranged from the evaluation of memory in rodents (Rebert et al. 1974) to assessment of cognitive divisions of the human mind (McAdam and Whitaker 1971). At the molecular level, an understanding of SP electrogenesis requires evaluation by the physiologist, neurochemist, and neuroanatomist of neural spiking patterns, synaptic transmitters, modulators, mediators and moderators, glial functions, ionic mechanisms, blood flow, energy metabolism, and macro- and microanatomy. Because of the variety, ubiquity and involvement of slow potentials in so many cerebral processes, the interdisciplinary study of SPs should greatly enhance the understanding of brain function in general. An outstanding question is whether SPs are mere signs of neurophysiological activity or whether they have a direct role in neural function *per se*. Some evidence suggests that the latter is true (Schmitt et al. 1976). If so, the study of SPs may contribute to our understanding of synthetic and integrative properties of the brain not easily accounted for in terms of digital information transmission systems. It is known that graded potentials at the neuronal level act to integrate converging inputs and provide a decision point in information flow. Might similar functions be attributed to SP events occurring at widespread points in the brain? The detailed explication of SP genesis will hopefully provide an answer to this intriguing question.

Has SP research contributed to the development of any general principles of brain function? The final section of this volume provides an impressive affirmative in the theories proposed by Cooper et al, Marczynski, Papakostopoulos, and Skinner. These general models are complemented by molecular models at the level of cellular membranes and ionic mechanisms proposed by Somjen and Libet (this section). These heuristic contributions are not surprising in view of the integrative nature of SP research. Slow potential phenomena thus appear to provide an increasingly important bridge between the mind and matter of the human brain.

SLOW POSTSYNAPTIC RESPONSES OF SYMPATHETIC GANGLION CELLS AS MODELS FOR SLOW POTENTIAL CHANGES IN THE BRAIN

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When Gerard and I initially explored the existence and significance of slow potentials (SPs) in the brain, we utilized the relatively simpler system available in the isolated cerebrum of the frog (Gerard and Libet 1940, Libet and Gerard 1941). The absence of vascular circulation eliminated any possible blood-brain SPs, and the thin-walled outer pallium of the cerebrum made it feasible to record and apply SPs across a layer of similarly oriented cerebral neurons. These studies led us to suggest that SPs were generated as gradients along the dendroaxonal axes of neurons and that substantial extracellular fields of current could be developed when this occurred in masses of similarly oriented neurons. In spite of many developments since that time, questions about the precise cellular origins and electrogenic processes for SPs are obviously still open ones.

In the late 1950's, my interest was aroused in the potentialities of an even simpler system as a model for SP mechanisms. Findings of slow potential responses to orthodromic inputs were being reported for isolated sympathetic ganglia (see Libet 1970). These structures have no complicating interneuronal networks (although the existence of one type of interneuron has now been established); they are quiescent except when activated by neuronal or chemical inputs; composition of external medium is easily manipulated; and the postsynaptic responses of the principal neurons or "ganglion cells" themselves can be readily studied. We have been able to establish that the ganglion cells can exhibit, in addition to the well-known excitatory postsynaptic potential (EPSP), a slow inhibitory postsynaptic potential (IPSP) and an even slower EPSP (Libet 1970). The unique features of these slow postsynaptic potentials (PSPs) and of an additional enduring modulatory action (Libet and Tosaka 1970) will now be listed, with a brief reference in each case to potential significance for SPs and for other slow functions of the brain.

Neuronal origin

Slow ganglionic potentials can be recorded with surface electrodes in response to brief trains of orthodromic, preganglionic volleys. These can be shown to be independent of the true afterpotentials that follow cell-firing by their appearance in the partially curarized ganglion (Fig. 1). In the latter the (fast) EPSPs are depressed to below firing level; superimposed upon and following each train of EPSPs is a surface-positive (hyperpolarizing) and a later surface-negative (depolarizing) slow potential. These slow potentials are also demonstrable by direct intracellular recordings in almost all cells proven to be principal neurons (i.e., ganglion cells, Fig. 2). The slow hyperpolarizing and depolarizing postsynaptic potentials (Fig. 2 II) are properly to be regarded as a s-IPSP and s-EPSP, respectively: they are obviously neuronal, not glial, in origin; they can be elicited independently, in the absence of any EPSPs (Fig. 2 II, tracings E,F); they are selectively blocked not by curare but by atropine (Fig. 2 II, tracings B-D) and, in the case of the s-IPSP, by an α-adrenergic antagonist; and they appropriately alter neuronal excitability (Libet 1964; Dunant and Dolivo 1967, Brimble and Wallis 1974). It is clear that true postsynaptic potentials with the slow timing features described below can be generated by a synaptic action at the single-cell level; the corollary is that an extracellularly recorded SP of neuronal origin need not be an envelope of a series of faster individual cell responses.

Repetitive input

Although a single orthodromic volley can elicit a relatively small s-IPSP and s-EPSP, the amplitudes and durations of these responses can be built up greatly by a repetition of 5 or 10 volleys (Fig. 1 and 2 II). Optimal repetitive frequency is about 10 to 20 per sec for the s-EPSP and about 40 per sec for the

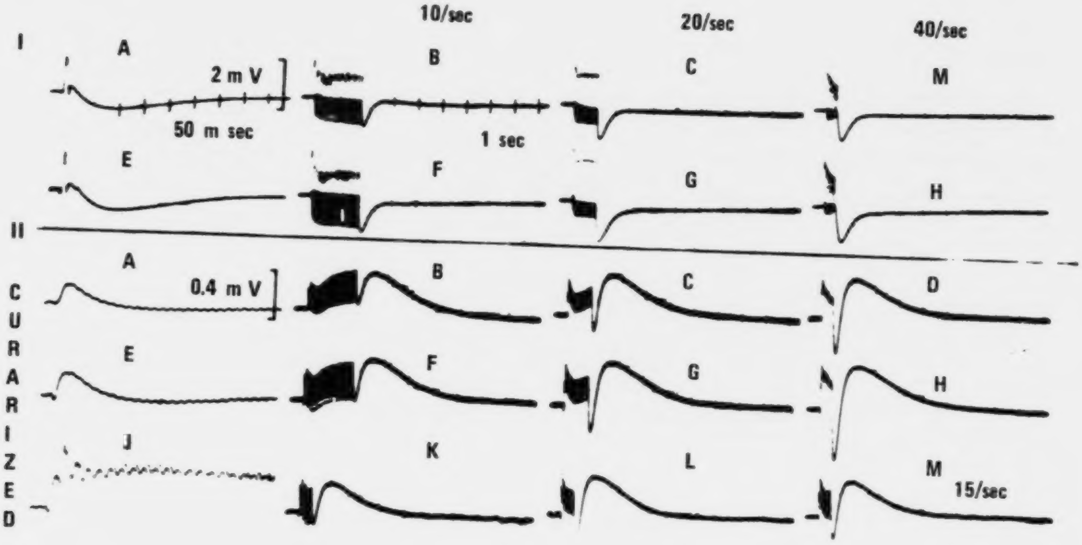

Fig. 1. Surface recordings of responses of isolated superior cervical ganglion (rabbit) to stimulation of preganglionic (cervical sympathetic) nerve. Upper section, I, taken before, and lower section, II at higher gain, after partial curarization. Responses are to a single volley (A,E), or to a train at the pulse frequency indicated and recorded at the slower sweep speed of l sec per div. (For the upper horizontal row in each section, stimulus intensity is below threshold for preganglionic C fibers; for lower rows, stimuli are supramaximal for both B and C fiber inputs.) Note the following points: (1) The compound action potential, and its surface-positive afterpotential, are absent in the curarized state; single responses in the latter consist of the (fast) EPSP (section II, A and E), and repetition at 40/sec produces a sustained EPSP with almost no spike components (J). (2) In spite of the absence of cell firing and of any true afterpotentials, the train responses of the curarized ganglion exhibit a slow surface-positive (hyperpolarizing) and an even slower surface-negative (depolarizing) component, superimposed on and outlasting the summated EPSPs produced during the stimulus train. These are the s-IPSP and s-EPSP, respectively. (3) Evidence of the slow depolarizing component is visible as a negative hump in the form of the posttetanic afterpotential of the firing, uncurarized ganglion. This hump can be selectively eliminated by atropine (see Libet 1964), with the positive after-potential then showing a long, exponential decay. (From Eccles and Libet 1961.)

s-IPSP, but increases are substantial even with 2-per-sec trains. This large effect of repetition appears to be a postsynaptic function, not a presynaptic one as in classical posttetanic potention (PTP): (1) It occurs without a parallel effect on the EPSP response. (2) The effective repetition interval is much longer than for presynaptic PTP. (3) Effective train durations are much shorter than for presynaptic PTP. The slow PSPs thus can exhibit considerable temporal facilitation with physiologically reasonable inputs, both as to frequency and duration of the arriving group of impulses.

Durations

The slow PSPs have durations from a few seconds after a single preganglionic volley to 10 to 30 sec following a brief train of 5 to 20 preganglionic volleys (at 2 to 40/sec). It should be reemphasized that these prolonged PSPs cannot be assigned to any sustained presynaptic delivery of acetylcholine (ACh); the fast EPSP, which is also cholinergic, shows a relatively sharp termination after the end of each brief preganglionic train. The long period of heightened excitability that accompanies the s-EPSP provides a form of *postsynaptic* PTP, which can summate with a heterosynaptic input (Libet 1964). This feature is far more significant for brain function than that of classical presynaptic PTP, which is only effective homosynaptically (i.e., when test volleys are delivered via the same fiber inputs that carried the train of conditioning volleys). There has been a tendency to regard as "modulatory" all synaptic changes that are slower than the classic PSPs. It would be better, however, to expand the view of possible types of excitatory and inhibitory synaptic actions so as not to exclude responses like the s-IPSP and s-EPSP simply on the basis of slower temporal properties or different electrogenic mechanisms. The term "modulatory" should be reserved for cases in which a transmitter alters the reactivity in a synaptic pathway by actions that go beyond the changes in cell excitability associated with its own PSP (see discussion under "Dopamine modulation..." below), and for the additional cases in which a

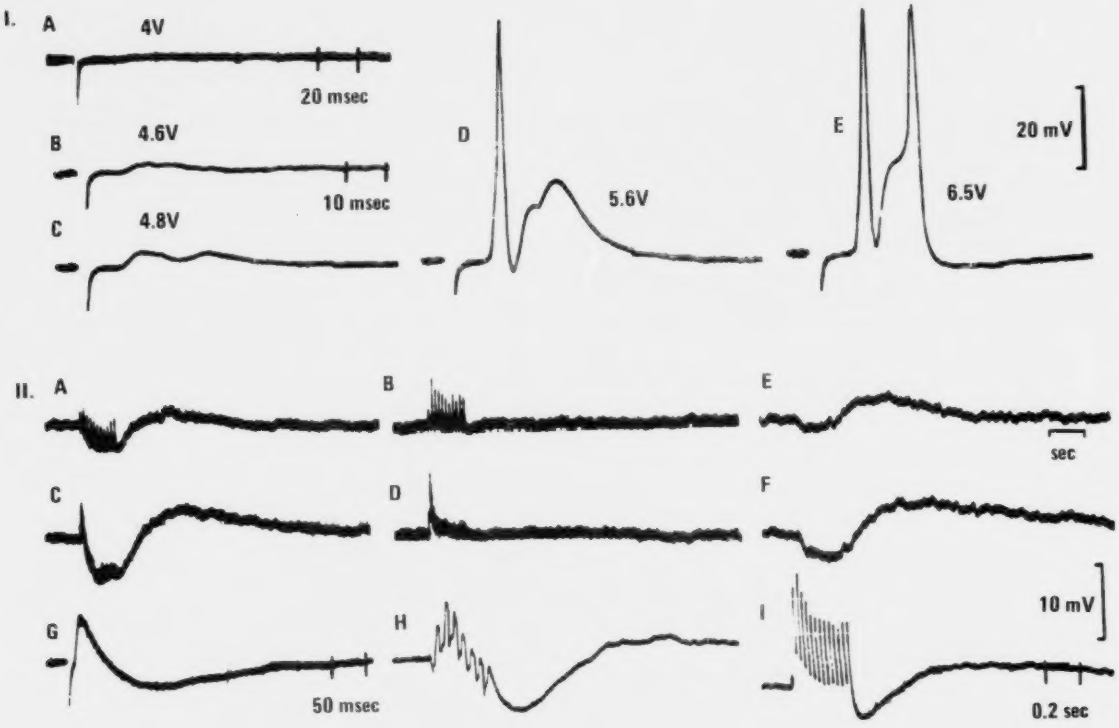

Fig. 2. Intracellular recordings from a principal neuron (ganglion cell) in rabbit SCG. Upper section, I: Responses of normal, uncurarized cell; successive fast EPSPs appear as the stimulus strength applied to the preganglionic nerve is raised, until the EPSPs reach firing level for both the earlier arriving B fiber input (D) and the later arriving C fibers (E). Lower section, II: Responses of curarized cells. In bottom row, note the single EPSP in G, with its small s-IPSP component building up with repetition in H and (at slower sweep in another cell) in I. Upper two rows at slow sweep (see 1-sec bar). Top row responses (A,B,E) are to 10/sec, 1-sec trains and second row (C,D,F) to 40/sec, 1-sec trains. In A and C, note the small fast EPSPs (mostly blocked by curare and having a spike-like appearance at this slow sweep), with the s-IPSP and s-EPSP superimposed and following these. In B and D, both slow PSPs have been eliminated by addition of atropine (0.3 μg/ml), leaving behind the fast EPSPs alone. In E and F, another cell, curarization is strong enough to block the fast EPSPs completely, but the cell still exhibits s-IPSP and s-EPSP responses. In both portions of figure note that the slow potentials are recorded in typical neurons that also exhibit fast EPSPs and firing, but that the slow PSPs are also producible independently of fast EPSPs and of firing. (From Libet and Tosaka 1969.)

"neurohormone" is delivered to the affected neuron via the blood stream rather than by presynaptic terminals in its vicinity.

Long synaptic delays

The slow PSPs have extraordinarily long synaptic delays, in marked contrast to all the known delays for all fast PSPs, which are on the order of 1 msec or less (Eccles 1964). In mammalian ganglia, the delay for the s-IPSP is about 25 msec (80 to 100 msec in amphibian ganglia), and for the s-EPSP, it is in the range of 200 to 300 msec (Libet 1967, 1970); an example of the latter is seen in Fig. 3. It should be emphasized that these are delays between the arrival of the impulse in the preganglionic fiber terminals and the onset of the PSPs themselves; they are not delays in cell discharge. Furthermore, the delays are for PSPs mediated by only one (s-EPSP) or at most two (s-IPSP) synaptic steps in the ganglion; they are not due to the addition of many short delays in an interneuronal chain. Such delays and durations of response could easily accommodate the possibility that slow event-related potentials (ERPs) in the brain, like the P300 wave or the contingent negative variation (CNV), are developed by a single class of neurons activated monosynaptically. It should also be obvious that the traditional method for estimating the number of successive interneurons in a pathway–dividing the net central delay by about 0.5 to 1 msec for the assumed delay at each junction – could be invalid by a factor of two orders of magnitude!

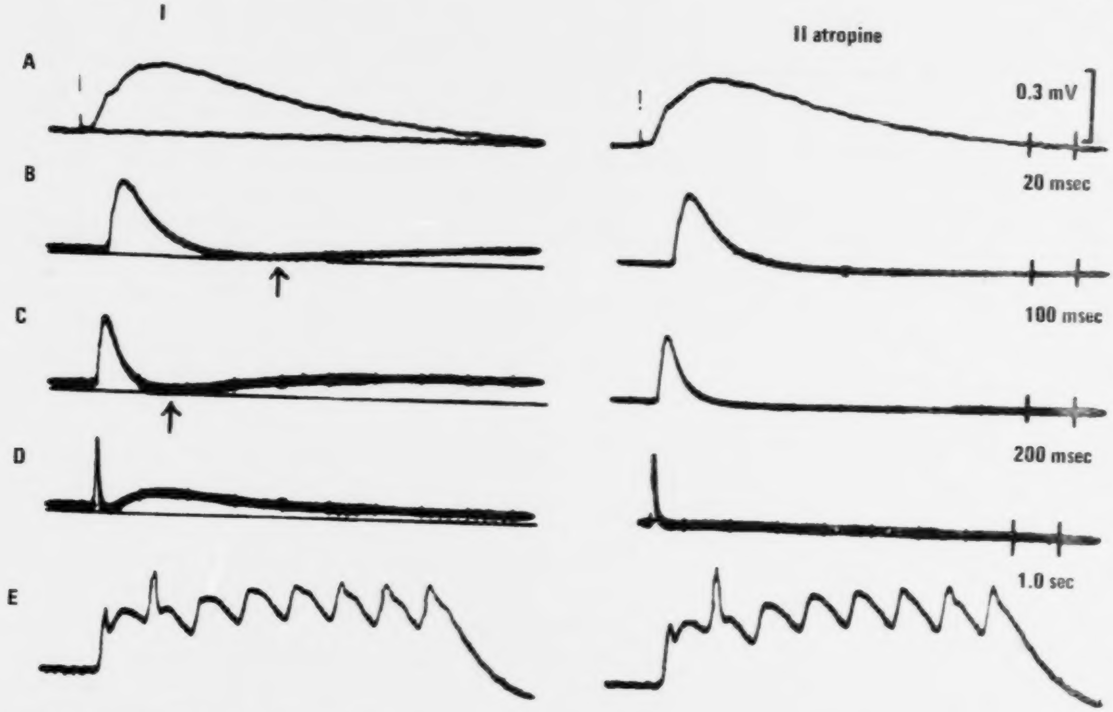

Fig. 3. Synaptic delays for (fast) EPSP vs. s-EPSP. Surface-recorded responses of curarized celiac ganglion of cat, column I before and column II after adding atropine (0.1 μg/ml). A-D show ganglionic responses to single preganglionic volleys at progressively slower sweep speeds. (E, at 50 msec per div, shows a brief train of responses, with only a small population action potential appearing on some.) Note that the onset of the s-EPSP is delayed until about 300 msec after the onset of the (fast) EPSP, as indicated by the arrows. The initial 5- to 6-msec latency before onset of the (fast) EPSP (see A) already includes conduction time into the presynaptic terminals of the preganglionic fibers here. Therefore, the extra 300-msec latency for the s-EPSP represents additional actual synaptic delay. (The relatively small amplitude of s-EPSP is due to use of a single volley rather than a train; but its reality is indicated by its selective elimination with atropine.) (From Libet 1967.)

Electrogenesis with no increases in membrane conductances

The slow PSPs do not depend on increases in membrane conductance for their electrogenesis, unlike all of the well-known (fast) IPSPs and EPSPs (Kobayashi and Libet 1968, 1974). In addition, changes produced by polarizing the resting membrane potential are not those expected on any ionic permeability hypothesis. Both the s-IPSP and s-EPSP responses are enlarged by increasing the resting membrane potential in the range of from -50 mV to about -65 or -70 mV and are rapidly decreased (but not reversed) by further hyperpolarization (Fig. 4); both are reduced rapidly by depolarizing to levels less than -50 mV, but this may be partly an indirect effect of a reduced membrane resistance associated with "delayed rectification." The actual electrogenic mechanisms for the slow PSPs are yet to be determined. They could involve activation of various ion pumps that may be electrogenic, although the specific case of the ouabain-sensitive Na^+-K^+ pump appears to be excluded (Kobayashi and Libet 1968, 1970; Libet 1970; Libet et al. 1977). It has been proposed that the s-EPSP may result from a decrease or "inactivation" in the resting membrane conductance for K^+, G_{K^+} (Weight and Votava 1970 for sympathetic ganglia, Krnjevic et al. 1971 for cerebral cortex, also see Krnjevic 1974), as opposed to the increases in ionic conductances for the fast PSPs. However, a careful evaluation of all the evidence disproves the validity of this proposal, at least for s-EPSPs in sympathetic ganglia (Kobayashi and Libet 1974, Libet and Kobayashi 1974).

The hypothesis that inactivation of G_{K^+} provides the electrogenic mechanism for the s-EPSP was initially based on findings of (1) an increase in membrane resistance (r_m) accompanying the s-EPSP in frog ganglion cells, and (2) a kind of reversal of the polarity of the s-EPSP when these same cells were hyperpolarized by passing steady currents across the membrane (Kobayashi and Libet 1968, 1970). But these characteristics are relatively restricted to the case of frog ganglion cells to which nicotine

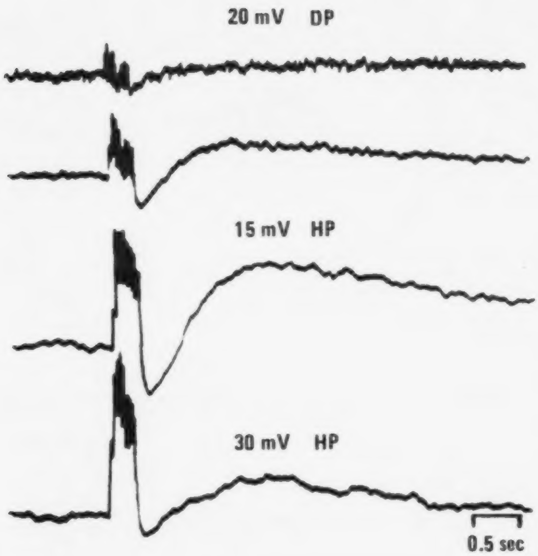

Fig. 4. Effects of polarizing currents on slow PSPs. Intracellular recordings of ganglion cell in rabbit superior cervical, partially curarized; each tracing is response to 0.25-sec train of supramaximal preganglionic volleys at 40/sec. Top tracing, response during continuous outward current, with resting membrane potential depolarized by 20 mV; second tracing, with no polarizing current (resting potential of this impaled cell = -45 mV); third tracing, during passage of inward current that hyperpolarized by 15 mV (i.e., present membrane potential kept at -60 mV); bottom tracing, during hyperpolarization of 30 mV (membrane potential at -75 mV). Note: (1) The summated EPSPs produced during each train increase progressively as the transmembrane potential is increased, as expected. (2) The s-IPSP and s-EPSP responses both increased with moderate increases in membrane potential, but both decreased with hyperpolarizing levels greater than the presumed normal or physiological resting potential of -60 to -70 mV. (From Kobayashi and Libet 1968.)

has been applied (for the purpose of blocking the fast EPSP responses). In curarized frog cells, there is either a small or no change in r_m during the s-EPSP (Kobayashi and Libet 1970); hyperpolarizing these cells produces no reversal of s-EPSP at all, but rather an enhancement of its late phase (Kobayashi and Libet 1974). Curarized mammalian ganglion cells show no detectable changes in r_m with the s-EPSP, and moderate hyperpolarization produces an increase, rather than the predicted decrease, in the amplitude of the s-EPSP (Kobayashi and Libet 1968; see Fig. 4). Even in the nicotinized frog cells, an increase in r_m with s-EPSP is found only when the cell membrane is depolarized. At normal or hyperpolarized levels, no change in r_m accompanied the s-EPSP response (Nishi et al. 1969). Additionally, the apparent "reversal" of polarity of the s-EPSP when nicotinized frog cells are hyperpolarized is not a true reversal; only a brief initial portion of the response reverses polarity, and the latency of this portion is distinctly shorter than that of the normal s-EPSP (Kobayashi and Libet 1970, 1974). Finally, the s-EPSP of nicotinized frog cells does not behave appropriately in relation to E_{K^+} (equilibrium potential for K^+); the apparent "reversal" of initial phase of s-EPSP has been found to occur at membrane potentials different from E_{K^+} (Kobayashi and Libet 1974), and the s-EPSP is relatively insensitive to the removal of K^+ from the external medium (Kobayashi and Libet 1968, Nishi et al. 1969).

A related proposal for generation of the s-IPSP involves an inactivation of resting conductance for Na^+, G_{Na^+} (Weight and Padjen 1973a). But the evidence for this hypothesis is all based on studies of nicotinized ganglion cells of frog, in which ACh is able to elicit a hyperpolarizing response by a direct postsynaptic action on ganglion cells (Weight and Padjen 1973b, Libet and Kobayashi 1974); this form of "s-IPSP" appears to be an abnormal component of the response, made possible by an interesting pharmacological interaction between side-effects of nicotine and ACh (Libet and Kobayashi 1974). In frog or rabbit cells treated with a "cleaner," a competitive nicotinic blocker like curare, the direct transmitter for the s-IPSP is a catecholamine (Libet and Kobayashi 1974); the latter must be released by an indirect action of ACh on an interneuron (Libet 1970, Libet and Kobayashi 1974). The physiological s-IPSP mediated by a catecholamine is obviously a different type of response from the ACh-hyperpolarization elicited in nicotinized frog ganglia. The characteristics of this response (Kobayashi and Libet 1968, 1970) and of non-nicotinized cells do not fit with the requirements of the G_{Na^+} inactivation hypothesis (Libet and Kobayashi 1974).

Whether an inactivation (decrease) of resting ionic conductances underlies those slow postsynaptic responses found in the central nervous system remains to be seen. Pyramidal cells in neocortex exhibit a slow muscarinic depolarizing response to ACh applied iontophoretically (Krnjevic and Schwartz 1967, Krnjevic 1974). This response strongly resembles the s-EPSP of mammalian sympathetic ganglion cells (see Marczynski, this section), except for a reported increase in r_m (Krnjevic et al. 1971). Slow hyperpolarizing responses to norepinephrine have been described for spinal motoneurons (Engberg and Marshall 1973) and for cerebellar Purkinje cells (Siggins et al. 1971). These hyperpolarizing responses resemble in important ways the s-IPSP of sympathetic ganglion cells, except for reported increases in r_m. It is not clear at present whether electrogenic mechanisms for slow PSPs in the central nervous system are actually different from those in sympathetic ganglia, or whether the experimental conditions in central nervous system studies have introduced additional characteristics that may have a more pharmacological than physiological significance. For example, it is generally recognized that in tests with iontophoretic application of chemical agents the local concentrations are unknown and may be higher than those available in physiological inputs. Also, the exogenously applied agent can reach and act on sites other than those involved in normal local synaptic transmission; such sites may be nonsynaptic receptor sites on the same cell, with different response properties from the postsynaptic receptors, or sites on other types of adjacent cells which indirectly affect the function of the cell under study. One example of the latter is the production of presynaptic blockade by exogenously applied catecholamines; this could depress ongoing background excitatory inputs into a cell and thus indirectly result in a hyperpolarizing shift and a rise in r_m back to nonexcited levels (e.g., Jordan 1973).

In any case, it is generally agreed that there are at least no increases in ionic conductances (i.e., no decreases in r_m) in all the slow responses studied, and even this presents some unique implications for slow functions in the brain. It means that long-lasting active PSPs could be generated without the increased ionic leakages and possible alterations in cell concentration gradients that characterize the "fast" PSPs:

1. The cellular energy costs for slow potentials are thus greatly reduced.

2. Possible effects of otherwise altered extra-and intracellular changes in ionic concentrations are eliminated; for example, the rise in extracellular K^+ concentration that is an expected feature of sustained fast EPSPs would not be produced during slow PSPs.

3. The "anomalous" ways in which slow PSPs are altered by the passage of polarizing currents could result in effects of the latter on slow potentials of brain that are different from the effects predicted with electrogenic mechanisms based on changes in ionic permeability.

4. Additionally, the s-EPSP mechanism is selectively and relatively rapidly depressed by depressants of oxidative metabolism, such as dinitrophenol, sodium azide, cyanide, or simple anoxia (Kobayashi and Libet 1968).

This sensitivity of the s-EPSP to loss of oxidative energy supply, and its synaptic delay of 200 msec or more, point to the probable involvement of a sequence of chemical reactions in its electrogenesis. There is already evidence that the synthesis of cyclic GMP (guanosine 3′, 5′-monophosphate) is an early step in this mechanism (McAfee and Greengard 1972, Kebabian et al. 1975), but the succeeding reactions are yet to be unravelled (Libet et al. 1975). The special sensitivity of the s-EPSP to anoxia is reminiscent of a similar one for many cerebral processes, and is in contrast to the relative insensitivity of the fast PSPs in both ganglia and brain.

Transmitters mediating the slow PSPs

The intraganglionic pathways and transmitters for fast and slow PSPs are schematized in Fig.5.

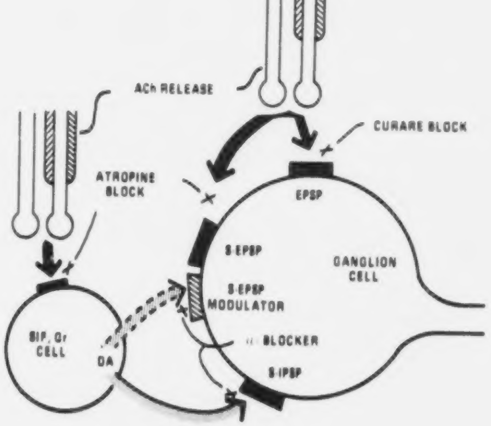

Fig. 5. Schema for synaptic mediation of fast EPSP, s-IPSP, and s-EPSP. Note: (1) The two types of postsynaptic receptors for ACh, nicotinic and muscarinic, on the same ganglion cell. (2) The small monoaminergic interneuron (SIF or granule-containing cell), which "converts" ACh input into a dopamine (DA) transmitter here. (3) The two actions of DA on the ganglion cell; these are represented in two types of receptors here, a concept supported by more recent evidence. (From Libet 1976.)

Muscarinic transmitter action for s-EPSP

The s-EPSP is elicited by a direct (monosynaptic) action of preganglionically released ACh on postsynaptic muscarinic receptor sites (Eccles and Libet 1961, Libet 1970). Deeper lying neocortical pyramidal cells have been found to exhibit a slow muscarinic depolarizing response to ACh, which has important similarities to the s-EPSP in ganglia. Indeed, most of the receptor sites involved in responses of cerebral neurons to ACh are also of the muscarinic type, and atropinic agents are potent modifiers of various brain functions. Evidence for participation of such responses in certain SPs and brain functions is summarized elsewhere in this symposium (Marczynski).

Adrenergic transmitter action for s-IPSP

The s-IPSP is elicited in ganglion cells by a direct action of dopamine, although exogenous norepinephrine can produce a similar response (Libet 1970, Libet and Tosaka 1970, Libet and Owman 1974). Dopamine is released by a special class of interneurons, now recognized as the small, intensely fluorescent (SIF) cells or, in electronmicroscope studies, as the small granule-containing cells. The SIF cells are activated by a muscarinic action of preganglionically released ACh (Eccles and Libet 1961, Libet 1970, Libet and Owman 1974). In the brain, it has been found that the norepinephrine transmitter delivered by fibers arising in the locus coeruleus can elicit a slow hyperpolarizing response in cerebellar Purkinje cells (Hoffer et al. 1972) and in hippocampal pyramidal cells; this response has important similarities to the s-IPSP of sympathetic ganglia. The cellular nature of the responses to various monamines elsewhere in the brain are yet to be worked out.

Dopamine modulation of the s-EPSP response to ACh

In addition to its role as an inhibtory transmitter in ganglia, dopamine was found to induce another neuronal change, which could persist for hours. This change is manifested in an enhancement of the response to ACh, but it is selective for the slow muscarinic or s-EPSP type of response (Libet and Tosaka 1970). This novel type of synaptic action, in which one transmitter alters the postsynaptic response to another, has now been shown to possess features of a memory process at the neuronal level (Libet et al. 1975). At least one cerebral example of such a modulatory action has already been reported (Yamamoto 1973). Also, a morphological substrate for monoaminergic actions, in the form of widespread cerebral distributions of various monoaminergic fibers that arise in certain brain stem nuclei, has more recently been provided. These nuclei have already been implicated in the control of sleep and waking states (Jouvet 1973), and the self-stimulation or "reward" mechanism of Olds (German and Bowden 1974). The notion has been gaining ground that these systems may in part function to change, in various ways, the reactive levels of cerebral neurons to other synaptic inputs (e.g., Jasper 1975, Reader et al. 1976). In the case of those ERP components or SPs in the brain that may be similar to the cholinergic, muscarinically mediated s-EPSP of ganglion cells, the possibility arises that monoamine inputs might produce long-lasting alterations in the amplitudes and durations of such ERPs produced at selective sites. Such modulatory changes by monoamine inputs could conceivably account for certain ERP changes which accompany psychological processes discussed elsewhere in this volume.

Acknowledgment

I dedicated this paper to Ralph Waldo Gerard, whose scientific imagination helped to pioneer the field of slow potentials in the central nervous system. The research was supported by Public Health Service Research Grant NB-00884 from the National Institute of Neurological and Communicative Disorders and Stroke.

CONTRIBUTION OF NEUROGLIA TO EXTRACELLULAR SUSTAINED POTENTIAL SHIFTS[1]

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Evidence for neuroglia acting as a generator of extracellular current

That sustained shifts of extracellular potential associated with protracted neural activity are, under certain definable experimental conditions generated, in part or entirely, by glial elements is indicated by two sets of observations. First, the time course of membrane potential changes of glia cells observed during neural activity is comparable to sustained shifts of extracellular potential. Second, extracellular potential shifts are altered by experimental manipulation in ways more similar to concomitant alterations of glial responses than to those of neurons.

In mammalian brains, membrane potential responses related to neural activity, but recorded from cells originally designated as "idle" or "unresponsive" and subsequently identified as glia, were first reported from the laboratory of Goldring (Sugaya et al. 1964; Karahashi and Goldring 1966; Castellucci and Goldring 1970; Ransom and Goldring 1973a, b, c). Kuffler and collaborators also described the properties and responses of neuroglia in leech and mudpuppy nervous systems (Kuffler and Potter 1964, Kuffler et al. 1966, Orkand et al. 1966).

The classical work of Kuffler's group has provided a theoretical outline of the possible mechanism of glial current generation. These investigators found that the membrane potential of glia cells conforms to the Nernst equation for potassium much more closely than that of neurons. In other words, the degree to which glial membranes favor permeation by potassium over other ions is significantly greater than the similar but lesser preference of neuronal membranes. Potential responses were observed in glia cells of the amphibian optic nerve, and it was suggested that they are related to presumed increments of extracellular potassium consequent to neural impulse activity. An electrotonic coupling between glia cells was, furthermore, demonstrated. The presence of low-resistance intercellular junctions was seen to provide the condition of glial contribution to electrical activity of tissue, for glia cells depolarized by external potassium could, through such junctions, draw current from distant, non-depolarized glia cells. The electric circuit would then be completed by return current flow through the extracellular medium. The latter would generate a voltage drop which could be registered by external electrodes.

A highly simplified model describing the behavior of such a quasi-syncytial electrotonic network has been developed (Joyner and Somjen 1974; Somjen 1973, 1974). The model is reproduced in Fig. 1 and 2. The elements of the model are: (1) a set of batteries representing the EMF of depolarized glia cells; (2) three sets of resistors simulating the conductances of glial cell membranes, the intercellular electrotonic junctions, and the extracellular medium; and (3) the bulk resistance of the body interposed between nervous system and reference (or ground). Capacitive components are ignored because the time course of the potential changes to be modeled is very long compared to the (probable) time constant of the circuit. The model demonstrates that the spatial profile of extracellular potential shifts would accurately map the spatial distribution of membrane responses (and, hence, of potassium accumulation) provided that the "space constant" of the network was small, i.e., membrane resistances were low compared to other resistive components. The profile of extracellular potential changes might extend beyond the spatial limit of

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[1] Since the adjective "slow" in electrophysiology can mean any event that lasts longer than 1 or 2 msec, it seems desirable to distinguish potential shifts that are maintained for seconds and/or rise and fall with half-times of 0.3 sec or more by another name. "Sustained potential" seems an accurate descriptive term. Processes that have an hourly or daily rhythm should be given still other names, for they probably represent yet different classes of events.

In cases where an electrical event has a known generator, that cellular element may justifiably be named. Thus, evoked sustained potentials of the spinal gray matter appear to be the sum of two components, a smaller abruptly rising neural potential (probably related to synaptic currents) and a larger, more slowly rising glial potential.

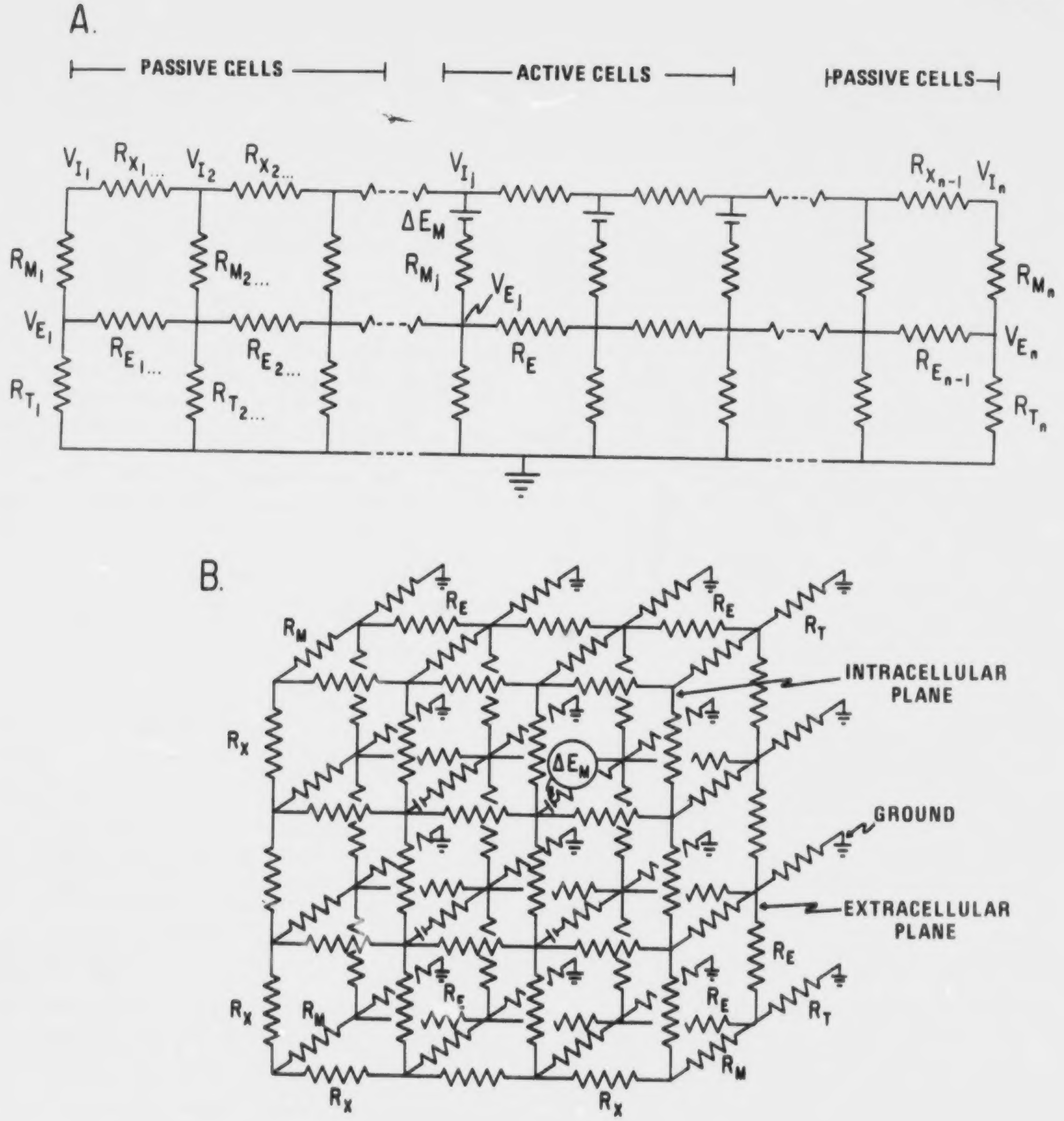

Fig. 1. Two models simulating electrotonic syncytia. A: Simulating a linear array of cells; B: A two-dimensional layer of cells. The cytoplasm of cells is assumed to be isoelectric, represented by the potentials at the points marked as V_I. Cells are assumed to be coupled by resistances, R_X, and connected to their environment by the membrane resistances R_M. The potential immediately outside the cells is given by V_E, and the environment of one cell connected to that of another by the extracellular resistances R_E. The extracellular fluid of the nervous system is grounded through the tissue resistances R_T. Some cells are assumed to be depolarized; these are designated "active," and the EMF of the potential change is represented by batteries ΔE_M. The resting potential of cells is not represented, since it does not contribute to current flow. Also neglected is membrane capacitance (see text). (After Joyner and Somjen, reproduced, by permission of the publisher, from Somjen 1973).

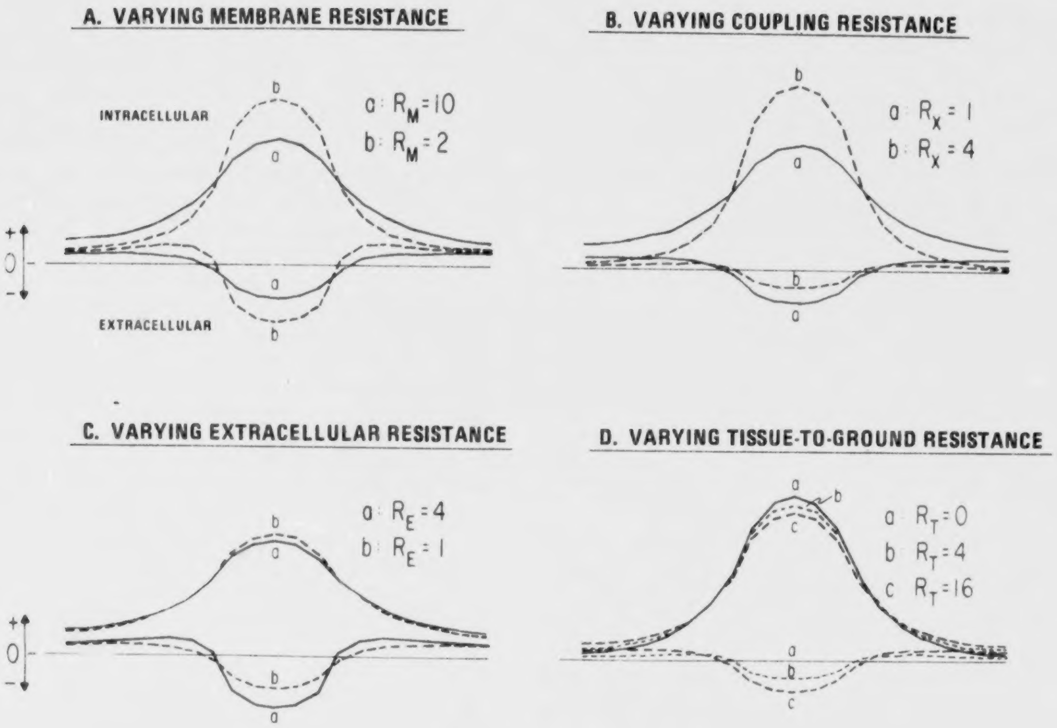

Fig. 2. Computer solutions of the model network of Fig. 1A. Twenty-one "cells" are represented, the central five of which are assumed to undergo depolarization. The voltage of the depolarizing effect is taken to be identical for all cases. The computer-generated profiles show intracellular and extracellular voltages referred to "ground," as they would be measured in conventional microelectrode recordings. The change of transmembrane potential would be given by the difference between intracellular and extracellular potentials shown. The absolute membrane potential would be the resting transmembrane potential (neglected in the model), less the change of transmembrane potential; i.e., the horizontal "zero" lines of the diagrams represent the "collapsed" resting membrane potential. In real cells the intracellular potential profiles would lie in the negative domain, below the zero line and below the extracellular potential profiles. Resistances that are not indicated in inset legends were assumed to be uniform within one set of computations. (After Joyner and Somjen, by permission of the publisher, from Somjen 1973.)

depolarizing EMF (the distribution of the "batteries" in the model) if the space constant were taken to be large (Fig. 2A). With the aid of the model, it also becomes apparent that a relatively small positive extracellular potential shift may or may not be detectable at the (inactive) extracellular "source" of current. It furthermore appears that the depolarization registered by an intracellular probe may fall short of the value predicted by the Nernst equation, even if the only charged particles admitted through the membrane were potassium ions. An erroneously low reading would always be expected if, as is sometimes done, intracellular potential responses were referred to a distant reference (or to ground) so that extracellular potential shifts were neglected (cf. Somjen 1975, Lothman and Somjen 1975). True attenuation of the transmembrane potential would occur if a significant fraction of current flow would spread well outside the activated region (note the cases of high membrane resistance and low coupling resistance in Fig. 2A and B).

The analysis of glial function by Kuffler and collaborators (Kuffler and Nicholls 1966) concerned the nervous system of cold-blooded organisms. For the mammalian central nervous system, experimental evidence now available supports the glial theory as follows:

1. The development of potassium-selective microelectrodes enabled the measurement of activity of this ion in central nervous tissue *in situ*. With these devices, it was shown that potassium activity can readily be induced to rise above resting levels significantly and reproducibly. Such responses can be evoked by electrical stimulation of tissue or afferent

paths leading to it (Vyskocil et al. 1972; Vyklicky et al. 1975; Krnjevic and Morris 1972, 1974; Kriz et al. 1974; Lux and Neher 1973; Somjen and Lothman 1974; Lothman et al. 1975; Lothman and Somjen 1975) and under more physiological conditions, e.g., in the visual cortex by "adequate" optical stimulation (Singer and Lux 1975). This response also occurs spontaneously during "spindle" activity in barbiturate anesthesia (Somjen et al. 1976).

2. A close correlation between depolarization of glia cells and sustained shifts of potential in the extracellular environment evoked by repetitive stimulation of afferent nerves was demonstrated in the spinal cord by Somjen (1970), Strittmatter and Somjen (1973), and Lothman and Somjen (1975). No such correlation exists for extracellular potential shifts and neuronal membrane potential responses (Somjen 1969, 1970).

3. Dependence of the membrane potential of mammalian glia cells on extracellular potassium activity was indicated by Pape and Katzman (1972) and Ransom and Goldring (1973a), and conformity of this relationship to the Nernst function by Lothman and Somjen (1975) for the spinal cord and by Pedley et al. (1976) in cortex.

4. The close correlation between transient elevation of potassium activity and sustained shifts of extracellular potential, evoked either by direct electrical stimulation of cortex (Lothman et al. 1975), by afferent nerve stimulation in gray (but not white) matter of spinal cord (Somjen and Lothman 1974, Lothman and Somjen 1975), or occurring spontaneously during seizure activity (Lothman and Somjen 1976) is also well documented.

The required electrical continuity of intracellular conduction within glial tissue of mammalian gray matter has not been demonstrated so far. Electrotonic junctions between glial cells have been shown only in invertebrate and cold-blooded vertebrate nervous systems (Kuffler and Potter 1964, Kuffler et al. 1966b, Cohen 1970).Yet, even if mammalian glia cells prove to be electrically insulated from each other, they could contribute to extracellular current flow, provided that the processes extend over sufficient distances in sufficient profusion to provide for cytoplasmic continuity between excited and quiescent regions. Müller cells of the retina and Bergman fibers of the cerebellar cortex fulfill this requirement. Only three-dimensional reconstructions from serial electron micrographs could determine the issue for other regions (Katchalsky et al. 1974, Somjen 1975).

In the mammalian nervous system, glial responses have been studied most intensively in the cerebral neocortex and in the spinal cord. Although qualitatively similar, the two regions appear to differ in the relative magnitude of response. In the spinal cord, the amplitude of glial depolarization is approximately twice the amplitude of the corresponding extracellular sustained potential shift. In the cortex, this ratio is consistently greater. Furthermore, in the spinal cord, smaller potassium transients appear to be associated with relatively larger electrical events than in cortex (reviewed in Somjen 1975). The close correspondence of the spatial profile of potassium responses and of sustained potential shifts in spinal cord (Lothman and Somjen 1975) indicates that the "space constant" of the glial network (see Fig. 2) is small (i.e., membrane resistance is low). The relatively large extracellular potential shifts observed in spinal gray matter suggest a higher tissue resistivity (in relation to membrane resistance and cytoplasmic coupling resistance) than that of cortical tissue.

Oxidative metabolic activity is another function normally tied closely to pertubations in the distribution of ions. Oxidative metabolism can be monitored by measuring the fluorescence of NADH in neocortex (Rosenthal and Jobsis 1971, Rosenthal and Somjen 1973, Lothman et al. 1975) or in hippocampus (Lewis and Schute 1975). The close coupling between | potassium | responses, | sustained |potential shifts, and oxidative activity is broken during convulsions, as though seizures placed a load on energy metabolism in excess of the demand made on active transport by extracellular potassium (Lothman et al. 1975, Somjen et al. 1976). The relationship of cellular oxidation and ion transport is illustrated schematically in Fig. 3.

Significance of potassium and of extracellular electric current flow for neural function

Even if neurons are less sensitive than glia cells to small elevations of extracellular potassium, potassium discharged by active cells should, theoretically, influence the membrane potential of inactive neighbors and synapses between them. Actual intracellular recordings made from neurons in spinal cord suggest an indifference to prevailing extracellular potential (Somjen 1970) and potassium activity (Lothman and Somjen 1975). Nerve cells appear to be controlled by specific synaptic transmitters. Any superimposed influence by changes of potassium activity appears to be negligible or undetectable in electrical recordings. Transient responses of extracellular potassium and extracellular electric current flow appear also to be of little significance in the generation of primary afferent depolarization and the attendant dorsal root potentials evoked by afferent nerve stimulation (Somjen 1970, 1973, 1974; Somjen and Lothman 1974, Lothman and Somjen 1975).

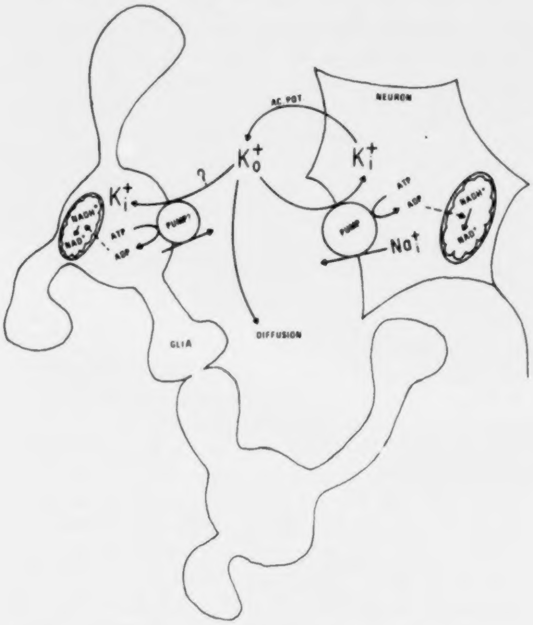

Fig. 3. Schematic representation of the relationship of perturbations of ion distribution and metabolic activity in central nervous tissue. Neurons lose potassium (and gain sodium) when firing action potentials and also during certain types of synaptic activity. All lost potassium must eventually be retrieved by neurons. Part of it may be recaptured immediately by active transport ("pump") through the neuronal cell membrane, but part may be temporarily dissipated by diffusion through extracellular space from high to low activity, and by uptake into glia. Active transport is fueled by Na^+-K^+ dependent membrane-bound ATPase. The ADP generated in the process enters mitochondria and activates the oxidation of NADH to NAD. NADH, being fluorescent, is accessible to optical monitoring. Events in the intramitochondrial enzyme chain lead to rephosphorylation of ADP to ATP, at the expense of oxygen and substrate utilization. Neuroglial membranes are also known to contain ATPase. Glia cells, like neurons, are exposed to the excess potassium accumulated in extracellular space but, unlike neurons, do not gain sodium in the course of activity. Whether or not glial ATPase is significantly stimulated by extracellular K^+ is not known at this time. Potassium dispersed either by way of the glial syncytium or by diffusion through extracellular space must eventually return by a reversal of the process. Note that extracellular space in central gray matter (unlike in diagram) occupies only about 15% of the tissue volume. (Reproduced by permission from Somjen et al. 1976.)*

During seizure activity, the distribution of potassium responses within the spinal cord shifts dramatically. Cells and fibers in ventral grey matter are exposed to potassium levels greatly in excess of that seen under normal conditions. These paroxysmal elevations of potassium may well be the agent responsible for paroxysmal dorsal root potentials which behave differently from dorsal root potentials evoked by afferent stimulation in normal spinal cords (Lothman and Somjen 1976).

The possibility that extracellular current generated by neurons may influence other neurons in the vicinity was much discussed a few decades ago (Libet and Gerard 1941; Terzuolo and Bullock 1956) and has not been resolved. The interactions of glia, neurons and $IK+I_o$ in physiological and pathological conditions are the subject of two forthcoming publications (Varon and Somjen, in press; Somjen, in press).

Validity of the glial model for the contingent negative variation and other event–related potentials

Potassium-induced depolarization of neuroglia is a candidate for supplying currents for potential deflections which can be measured only in seconds rather than milliseconds (half rise times and half decay times of 0.3 sec or more). Even for these it is not a unique source, for we have recorded small negative potential shifts in white matter and in dorsal roots of the spinal cord that were not associated with elevated potassium activity and were, nevertheless, sustained for seconds. Such non-potassium related potentials were small with sudden onset and decay compared to those related to potassium and glial depolarization.

Although not the only possible source of sustained extracellular current, neuroglia deserves special attention for two reasons: (1) glial theory has withstood rigorous experimental testing, albeit under limited and physiological conditions; (2) its role could be tested again, under more life-like circumstances.

In principle, the experimental testing of glial theory is simple. To validate glial theory, it is necessary to show that elevation of potassium activity and shift of potential are closely and reproducibly correlated. Construction of a potassium-sensitive electrode that can be used under conditions in which CNV can be induced will be difficult, but certainly possible. It will probably prove easier to record potassium activity in a CNV-eliciting situation than to record the intracellular potential of glia cells.

Source of extracellular potassium

The source of excess potassium to which the membrane potential of neuroglia responds is neuronal. The question is, what kind of neural activity is most likely to add potassium ions to extracellular fluid (ECF) at a rate that exceeds their clearance. If the glial theory of SP generation proves generally valid and if we can exactly define the conditions of potassium accumulation in ECF, we then shall understand the significance of SP shifts. While the relative contribution of possible sources has not yet been assayed, clues can be derived from the following three observations (Lothman and Somjen 1975): (1) No rise of potassium activity could be detected in dorsal white matter of the spinal cord near the entry zone of an excited dorsal root unless stimulation was intense enough to activate C-fibers; (2) potassium activity did not detectably increase in the ventral horn of the spinal cord when the ventral root was antidromically stimulated; (3) by contrast, sizable potassium responses (and sustained potential shifts) were readily evoked in substantia gelatinosa of the spinal cord, a region where spike potentials are rarely recorded. Neurons, though abundant, are rarely entered (by intracellular microelectrodes), while "unresponsive" (presumed glia) cells are quite frequently entered.

From these observations, one suspects that impulses carried in myelinated axons and the action potentials of the somata of large neurons contribute relatively little potassium to extracellular fluid. Hence, one must seek the source either in synaptic currents generated by dendritic trees, in the activity of unmyelinated fibers and axonal arborizations, or else in small neurons, the impulses of which are hard to detect and difficult to penetrate with microelectrodes (see also discussion in Varon and Somjen, in press). Furthermore, the possible contribution of non-spiking neurons cannot be discounted (Rowland, this section). Electrical activity of non-spiking neurons would, theoretically, be distinguishable from that of glia cells, for synaptic potentials and synaptic noise bear readily recognizable features (Somjen 1973, 1975).

The theory of glial generation is compatible with the theory of cholinergic mediation of event-related sustained potentials (Marczinsky, this section). In normal cortex under physiologic conditions, it is conceivable that the most abundant sources of potassium are activated by cholinergic input. The idea of direct action of ACh on the glial cell membrane is less attractive because it implies extrasynaptic diffusion of ACh in tissue rich in cholinesterase. Besides, depolarization by ACh is associated with a rise in membrane resistance (Krnjevic et al. 1971), and no such change was observed during the depolarizing response of glia cells associated with neural activation (Somjen 1970, Ransom and Goldring 1973b). Finally, the conformity of glial depolarization to the prediction of the Nernst equation leaves no requirement of an influence other than that exerted by potassium (Lothman and Somjen 1975).

NEUROCHEMICAL MECHANISMS IN THE GENESIS OF SLOW POTENTIALS: A REVIEW AND SOME CLINICAL IMPLICATIONS

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Since there is evidence that SPs are related to neuronal activity (Rebert 1973b, Rowland 1974), there is reason to consider whether particular neurohormonal substances are involved in their genesis. Several crucial questions arise in this connection. Is the concept of a neurotransmitter, which implies a brisk and quickly reversible effect on ionic transport across a neuronal membrane, compatible with a role in the genesis of SPs, or should our attention be directed to substances capable of acting as modulators rather than transmitters, i.e., to substances with slow onset of action and a sustained effect on neuronal and glia cell membranes? Can the influence of the ascending reticular activating system (ARAS) on epicortical (Caspers 1961) and subcortical SPs (Hayward et al. 1966) be related to a particular transmitter or modulator? What is the role in SPs of the cholinergic component of the ARAS, defined histologically by Shute and Lewis (1967, 1969) and pharmacologically by Bradley and his colleagues (Bradley 1958) and by Rinaldi and Himwich (1955)? Finally, is it possible to relate the neurohormonal mechanisms which underlie SPs to a general concept of information flow in the mammalian brain? (The latter question is discussed in the final section of this volume.)

Cholinergic mechanisms in epicortical negative SPs

The cholinergic component of the ARAS originating in the tegmental nuclei projects to the neocortex (Shute and Lewis 1967), and the release of acetylcholine (ACh) from the cortex is related to the tone of the ARAS (Mitchell 1963, Kanai and Szerb 1965, Celesia and Jasper 1966, Pepeu and Mantegazzini 1964). The role of ACh in EEG desynchronization has been postulated (Rinaldi and Himwich 1955, Phillis 1976) and, because surface negative SPs accompany ARAS stimulation (Arduini 1958), a role in SP genesis is also possible.

If ACh is involved in SP genesis, an important question concerns the type of cholinergic receptors (muscarinic or nicotinic) that mediate its effect. There is strong evidence that the apical dendrites of some neurons in the neocortex are endowed with depolarizing muscarinic receptors that can be selectively blocked by atropine (Sigg et al. 1965). One can assume with reasonable certainty that these dendrites belong to large pyramidal cells located between layers IV and V which are not sensitive to nicotine, but are very responsive (in terms of spike generation) to iontophoretic application of ACh. These neurons are endowed with "pure" muscarinic receptors that can be blocked by atropine or scopolamine applied topically or systemically (Krnjevic and Phillis 1963, Krnjevic 1974). Some cortical neurons are not excited by ACh, and others are even inhibited by micro-iontophoretic application of ACh (Phillis 1976). Hence, the question arises as to whether the cholinoceptive "minority" of large pyramidal cells is capable of determining the surface negative SP upon release of ACh from terminals of ARAS projections.

Several observations support an affirmative answer to this question. First, tracing the polysynaptic cholinergic ARAS projections to the neocortex in the rat and monkey, Shute and Lewis (1967, 1969) showed that these projections relay in the septal region. In addition, Pirch and Norton (1967b) demonstrated that rats with septal lesions show significantly smaller negative SPs in response to conditional stimuli than do normal animals. Secondly, laminar recording of SPs in cortex treated with various concentrations of ACh showed that the initial surface negativity rapidly spread to deeper layers and reached its maximum at the level of large pyramidal cells, or layers IV and V (Ferguson and Jasper 1971). Finally, the pharmacological study of surface negative long-latency components of sensory-evoked potentials and concomitant measurements of ACh release clearly point to causal relationships between ACh output and the amplitude and duration of the negative waves. Topical application of low concentrations of cholinesterase inhibitors prolonged the duration and increased the amplitude, while hemicholinium-3, which is known to interfere with choline uptake and ACh synthesis, blocked the negative waves. A similar blocking effect can be produced by application of antimuscarinic drugs (Szerb 1965). These data strongly indicate that ACh is released presynaptically in the cortex from cholinergic components of the ARAS originating in tegmental nuclei, and that ACh plays a significant role in the genesis of surface-negative SPs. A state of hyperarousal associated with sustained depolarization of apical dendrites, however, may reduce event-related negative SPs (*vide infra*).

Functional differences between muscarinic and nicotinic receptors

Cholinoceptive neurons excited by ACh in the cortex, caudate nucleus, thalamus, and hypothalamus show responses to ACh markedly different from those of Renshaw cells in the spinal cord, which are endowed predominantly with nicotinic receptors. ACh applied to the the latter neurons acts as a typical transmitter: excitation of Renshaw cells is almost instantaneous and lasts only as long as administration of ACh (the late and prolonged response caused by activation of muscarinic receptors is usually negligible). On the other hand, the response of neurons with predominantly muscarinic receptors is slow in onset and outlasts the application of ACh for many seconds and even minutes (Krnjevic 1974). Moreover, ionic mechanisms of ACh action on membranes with muscarinic receptors are substantially different from those with nicotinic receptors. In the former instance, ACh reduces the potassium current during the late phase of the action potential. This reduction results in delayed repolarization after each action potential and in increased membrane resistance (Krnjevic 1974). Thus, cortical neurons "primed" with ACh in subthreshold concentrations show a long-lasting lower threshold to incoming volleys or to application of excitatory amino acids, and a tendency to repetitive firing that can be blocked by antimuscarinic drugs. Therefore, the effect of ACh on neurons with muscarinic receptors can be better described as a modulator rather than transmitter action.

In view of the physiological role of cholinergic mechanisms at the cortical level and their contribution to the genesis of negative SPs, it should be mentioned that ARAS-induced facilitation of neuronal responses to visual stimuli can be mimicked with micro-iontophoretic application of ACh. Moreover, both facilitatory influences can be blocked by antimuscarinic drugs (Spehlmann 1971). This observation and the negative SPs induced by increased tonus of the ARAS associated with the release of ACh suggest that the diminishing gradient of negativity toward the depth of the cortex should be associated with an overall reduced threshold to sensory volleys and enhanced firing of most cortical neurons. This conclusion is not in agreement with Fromm and Bond (1964), but agrees well with Rowland's data (1974) and with our own observations that surface positivity as well as deep positivity, accompanied by alpha-like oscillations, are always correlated with conspicuous inhibition of neuronal firing in freely moving animals during operantly conditioned behavior (Marczynski and Karmos, this volume).

Most likely, there are no substantial differences in the neurohormonal mechanisms of SPs that are topographically restricted to specific sensory projections, e.g., those described by Gumnit and Grossman (1961) and Picton (this volume) over the auditory cortex, compared with negative SPs distributed diffusely over larger cortical regions. An enhanced release of ACh, topographically restricted to the visual cortex, is observed in response to visual stimuli while the remaining cortical regions show only moderate enhancement of ACh release (Collier and Mitchell 1966, Neal et al. 1968). Our studies in cats show that both types of SPs are almost equally sensitive to systemic administration of antimuscarinic drugs (Marczynski, unpublished).

Results of pharmacological studies of CNV in man are in harmony with cholinergic mechanisms discussed above. Atropine (0.4 to 0.5 mg, i.m.) markedly reduced the mean amplitude of CNV, while small doses of nicotine, taken in cigarette smoke, increased these SPs in subjects classified on the basis of psychological tests as extroverted (Thompson et al., this volume; Ashton et al. 1974). Since cortical cholinoceptive neurons in man, like those in experimental animals, are most likely endowed with "pure" muscarinic receptors and, therefore, are not sensitive to nicotine, the locus of nicotinic action is probably restricted to the midbrain part of the ARAS or to the pons as shown in cats and dogs (Kawamura and Domino, 1969; Knapp and Domino, 1962).

Catecholaminergic systems and SPs

Norepinephrine (NE) pathways originate in tegmental nuclei and project to midbrain and forebrain structures, including n. ventralis anterior (VA) and n. reticularis (R) of the thalamus (Fuxe 1965). VA and R regulate thalamocortical EEG synchronization by generating rhythmic sequences of IPSPs in neurons of specific thalamic relay nuclei (Sasaki et al. 1976; Frigyesi 1972; Skinner, this volume). Since NE projections to most areas, including the thalamus and cortex, may be regarded as inhibitory (Hoffer and Bloom 1976), NE-mediated modulation of inhibitory neurons in R and VA may be of crucial significance in normal functioning of the sensory gating system and selective attention. NE terminals, present in all areas of neocortex, arise from cell bodies located in the tegmental nuclei. NE axons run through the medial forebrain bundle, bypass the septal region, and project diffusely to the cortex (Fuxe et al. 1968).

Dopaminergic (DA) neurons with cell bodies in the midbrain also contribute to innervation of large cortical areas, including the frontal region (Fuxe et al. 1974, Lindvall et al. 1974, Berger et al. 1974). These DA projections may be as important in the regulation of integrative processes as the DA projections to the limbic and mesolimbic areas described by Ungerstedt (1971).

At the cortical level, the function of NE and DA terminals may be different. NE terminals establish contacts preferentially with apical dendrites of pyramidal cells and, therefore, have a distribution characteristic of nonspecific afferents (Fuxe et al. 1968). On the other hand, DA terminals in frontal cortex, entorhinal cortex, and pyriform cortex show highest density in deeper layers, particularly V and VI. Only in the cingulate gyrus do DA terminals show a distribution comparable to that of NE terminals–i.e., highest density in layers I, II, and III (Lindvall et al. 1974, Berger et al. 1974).

Experimental evidence indicates that, at the thalamocortical level, catecholaminergic projections may influence the genesis of SPs by inhibitory action on inhibitory interneurons that are responsible for the phasing of EEG activity and positive SPs. Alternatively, these projections may modulate the sensitivity of excitatory cholinergic receptors of the muscarinic type, present at the membrane of cortical pyramidal cells and their apical dendrites. Both mechanisms, which are of great clinical importance, are dicussed below.

Catecholaminergic modulation of GABA-mediated hyperpolarizing inhibition

Surface positive SPs are believed to reflect the hyperpolarization of large pyramidal cells and their dendrites (Creutzfeldt et al. 1969; Marczynski and Karmos, this volume).

The following observations support the contention that recurrent inhibition of cortical pyramidal cells (as well as thalamic relay neurons) is mediated by GABA-ergic neurons, which, in turn, are modulated by inhibitory catecholaminergic projections. These relationships are illustrated in a diagram of information flow in the mammalian brain (Marczynski, this volume). (1) Micro-iontophoretic application of GABA to pyramidal cells lowers membrane resistance and causes inhibitory postsynaptic potentials (IPSPs) whose patterns and time course are virtually identical with spontaneous IPSPs or those elicited by antidromic stimulation of the pyramidal tract that activates the inhibitory interneurons via axon collaterals (Krnjevic 1974, Johnston 1976). (2) The highest concentration of GABA-forming neurons (i.e., those that contain glutamine decarboxylase) is found in layers III and IV (Albers and Brady 1959), where inhibitory basket cells are located (Marin-Padilla 1975). (3) GABA is released from the cortex only during EEG synchronization (Jasper and Koyama 1969) when inhibitory interneurons show bursts of action potentials that coincide with inhibition of pyramidal cells (Steriade and Deschenes 1973). By contrast, GABA release from the cortex is totally suppressed during strong arousal or electrical stimulation of the ARAS associated with EEG desynchronization. During that time, inhibitory interneurons are suppressed (Steriade and Deschenes 1973). (4) Iontophoretic application of NE to cortical, as well as cerebellar, neurons and electrical stimulation of tegmental nuclei from which NE projections originate (e.g., n. coeruleus) elicit IPSPs with different characteristics from those induced by GABA (Hoffer and Bloom 1976). (5) GABA releasing inhibitory neurons (e.g., Purkinje cells of the cerebellum) are under powerful inhibitory control of NE projections from n. coeruleus from which a substantial contingent of both neocortical and thalamic NE projections also arise (Hoffer and Bloom 1976).

In conclusion, despite the lack of direct evidence, there are strong indications that the function of catecholaminergic terminals in deeper cortical layers is restricted to the process of disinhibition by suppressant action on the inhibitory interneurons in the recurrent circuits responsible for the phasing of EEG patterns. Since rhythmic phasing of neuronal activity in the cortex and thalamus is associated with hyperpolarization of large neuron populations (Andersen and Andersson 1968), and with surface positive SPs (Marczynski and Karmos, this volume), catecholaminergic modulation of the GABA releasing system may play an important role in the genesis and topographical distribution of SPs.

Catecholaminergic modulation of thalamocortical recruiting responses

Recurrent hyperpolarizing inhibition in specific thalamic relay nuclei, as well as the powerful inhibition generated by R and VA, is most likely GABA-mediated (Curtis and Johnston 1974). Thalamocortical recruiting responses and EEG synchronization depend on the integrity of these pools of inhibitory neurons (Skinner, this volume) and there is evidence that a catecholaminergic component of the ARAS modulates their function. First, IPSPs in thalamic relay nuclei are abolished during increased tonus of the ARAS (Purpura et al. 1966). At the same time, rhythmic firing of inhibitory interneurons is suppressed (Steriade and Deschenes 1973). Secondly, spontaneous arousal and electrical stimulation of the ARAS are associated with a large positive SP in R, which reflects tonic hyperpolarizing inhibition of this nucleus (Skinner, this volume). Thirdly, the catecholaminergic component of the ARAS projects diffusely to R and VA (Fuxe 1965). Finally, physostigmine-induced activation of the ARAS and the resulting blockade of thalamocortical recruiting responses can be prevented by depletion of catecholamines (VanMeter and Karczmar 1971).

Excitatory influences from frontal association cortex impinging on inhibitory pools of neurons in R, which, in turn, project to specific thalamic relay nuclei, determine the gating of sensory input–a mechanism which may be the basis for selective attention (Skinner, this volume). Sensory gating requires very selective, well-timed excitation of neurons in R which can only be effective if there is a moderate inhibitory background in this nucleus. The inhibitory surround is most likely provided by catecholaminergic projections.

Catecholaminergic activation of subcortical cholinergic system

In the cat preparation with the brainstem transected at the midpontine pretrigeminal level, d-amphetamine administered systemically increases ACh output from the cortex (Nistri et al. 1972). This effect could be prevented by septal lesion or pretreatment of the animal with alpha-methyl-p-tyrosine, a drug that blocks synthesis of NE and DA. Apparently, such activation of the ACh system does not depend on the integrity of brainstem ARAS nuclei since (1) pentobarbital does not block the effect of amphetamine on ACh output even in doses that block EEG activation and ACh output in response to electrical stimulation of the ARAS and (2) amphetamine activates EEG patterns and increases ACh output in cats transected at the pretentorial level, a preparation which excludes nuclei from which the cholinergic component of the ARAS originates (Nistri et al. 1972). Amphetamine, however, also activates EEG patterns in cats with septal lesions in which no cortical enhancement of ACh output is observed. This puzzling observation can be explained by the previously discussed possibility that amphetamine, by activating the catecholaminergic system, may suppress the GABA-ergic inhibitory pools of neurons in the thalamus and cortex, thus preventing the emergence of synchronized EEG patterns.

Cholinergic mechanisms of subcortical SPs

Neuronal mechanisms

Large negative SPs have been observed in the thalamus and other subcortical areas during the reaction time foreperiod (McCallum et al. 1973; Rebert 1972, 1973b) and in response to electrical stimulation of the ARAS (Hayward et al. 1966). These SPs seem to reflect ARAS modulation of transmission in sensory thalamic nuclei. Evidence from the microelectrophoretic studies of the lateral geniculate (Steiner 1968), the ventrobasal nuclei (McCance et al. 1968), and the medial geniculate (Tebecis 1970) show that the effect of electrical stimulation of the ARAS can be mimicked by ACh application, and that both effects can be blocked by antimuscarinic drugs given systemically or applied topically. These studies suggest that the cholinergic ARAS component exerts a strong facilitatory effect on sensory transmission. Since negative SPs in specific thalamic nuclei closely mirror frequency of neuronal firing (Rebert 1973b), it appears probable that these SPs reflect increased excitability of relay neurons in response to afferent input, an effect that is likely to be mediated by activation of cholinergic ARAS pathways.

Participation of glia cells

Preliminary observations (Krnjevic 1974) show that iontophoretic application of ACh to cells identified as glia causes a slow onset and prolonged depolarization that outlasts the application of ACh by many minutes. At the same time, there is an increase in membrane resistance–i.e., an effect strikingly similar to that seen in neurons with muscarinic receptors. If this is a general property of glia cell behavior, it could help explain the genesis of SPs in both cortical and subcortical areas and could account for certain discrepancies between neuronal firing patterns and SPs, e.g., those observed by Rebert (1973b) in the lateral geniculate.

Are glia cells depolarized by ACh, or is glia cell depolarization secondary to an increase in extracellular potassium caused by neuronal firing? The increase of membrane resistance in both glia cells and neurons upon application of ACh (Krnjevic 1974) suggests an independent sensitivity to ACh. Rowland (1974) has also suggested that the depolarization of glia cells in response to ACh release may account for negative SPs without obvious correlation with grossly integrated multi-unit activity in some regions of the brain. Somjen (this section) discusses in detail the possible contribution of glia cells to SPs.

Genesis and pharmacology of positive epicortical SPs

Common features of surface positive SPs

Most positive SPs in man, such as the P300, P450, skilled performance positivity (SPP) described by Papakostopoulos et al. (this volume), and detection positivity (DP) of Cooper et al. (this volume) increase in amplitude with greater *a priori* uncertainty of outcome of performance and/or greater difficulty in correct event recognition. The unusually large SPP and DP apparently reflect the demanding task involved in the eliciting paradigm. If the *a priori* uncertainty is held constant, positive SPs in most instances increase in proportion to the *a posteriori* reduction of uncertainty, i.e., when there is less doubt that the performance was successful (Ruchkin and Sutton, this volume). In the cat, the level of *a priori* uncertainty also plays a major role in the emergence of reward contingent positive variation (RCPV) recorded over the parieto-occipital cortex (Marczynski et al. 1969, 1971a). Presentation of milk triggers an augmented RCPV when the reinforcement schedule for bar pressing is variable (i.e., unpredictable) in comparison to a schedule in which all bar presses are rewarded (Marczynski and Burns 1976). RCPV is, however, more sensitive to *a posteriori* reduction of uncertainty. For instance, as shown in Fig. 1, when an animal finds that there is a perfect match between the expected and actual result of a lever press, RCPVs are of greater amplitude. If, however, the animal expects pure milk, but receives water or adulterated milk in-

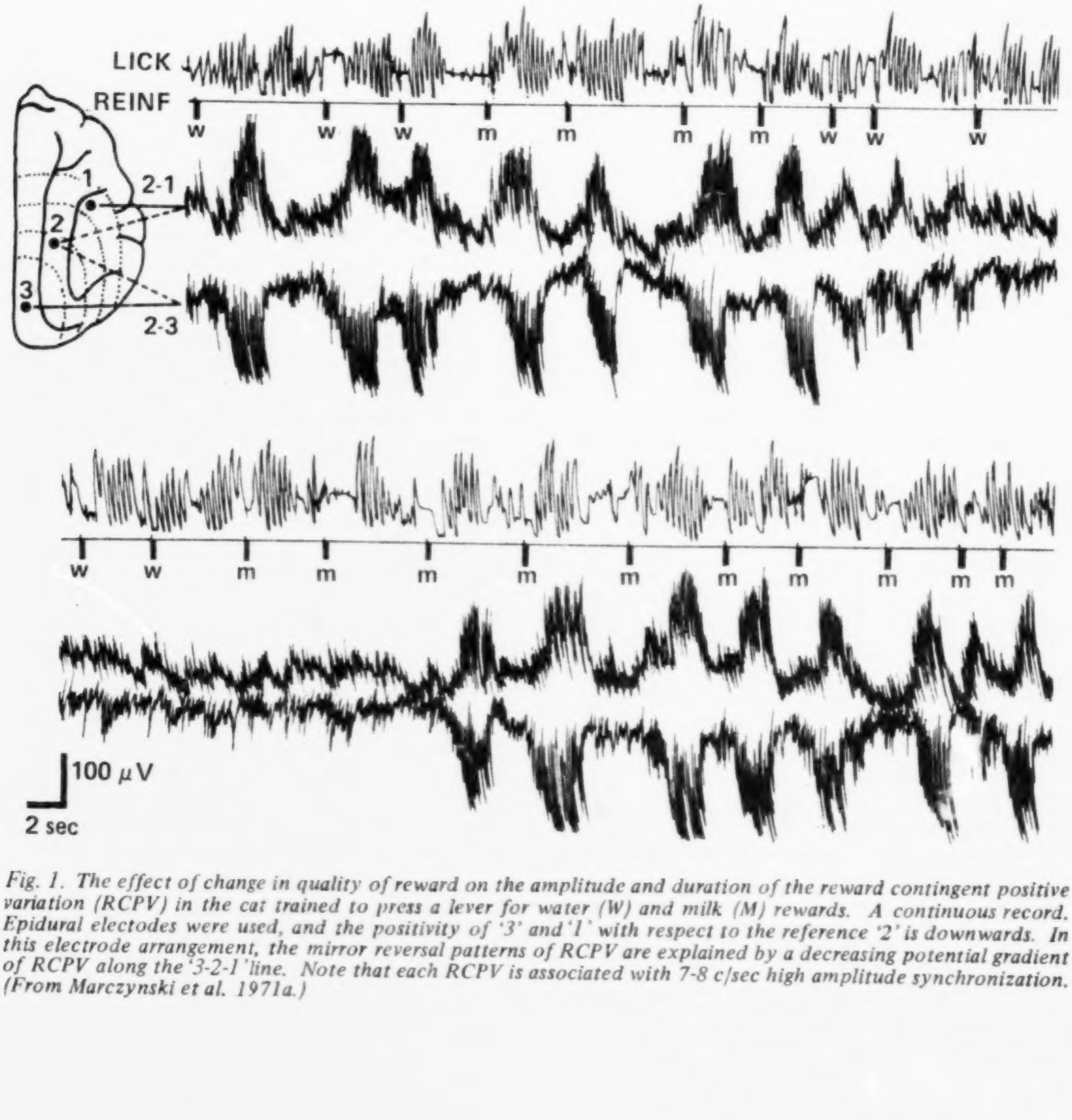

Fig. 1. The effect of change in quality of reward on the amplitude and duration of the reward contingent positive variation (RCPV) in the cat trained to press a lever for water (W) and milk (M) rewards. A continuous record. Epidural electodes were used, and the positivity of '3' and '1' with respect to the reference '2' is downwards. In this electrode arrangement, the mirror reversal patterns of RCPV are explained by a decreasing potential gradient of RCPV along the '3-2-1' line. Note that each RCPV is associated with 7-8 c/sec high amplitude synchronization. (From Marczynski et al. 1971a.)

stead, the electrocorticogram (ECoG) synchronization (Sterman and Wyrwicka 1967) and associated RCPV are suppressed or blocked (Marczynski et al. 1969, 1971a,b).

There is substantial evidence that all longer-duration surface positive SPs result from hyperpolarizing inhibition of pyramidal cells and the electrotonic spread of IPSPs to apical dendrites (Creutzfeldt et al. 1969). Hyperpolarization results from recurrent and, perhaps, feed-forward inhibitory phasing of neuronal activity, as indicated by the relationships between inhibitory neuronal discharge, the time course of IPSPs (Steriade and Deschenes 1973), and firing patterns of neurons during emergence of the RCPV (Marczynski and Karmos, this volume). The close correlation between cortical release of GABA and level of cortical EEG synchronization (Jasper and Koyama 1969) supports this interpretation. Since inhibitory neurons in the cortex and thalamus are themselves subject to inhibitory modulation by the ARAS (vide supra), the general conclusion can be drawn that all aforementioned positive SPs occur during a transient but powerful suppression of the ARAS by influences originating in the forebrain (Marczynski, this volume). Electrophysiological evidence for ARAS suppression during emergence of the RCPV is convincing (Marczynski and Hackett 1969, Hackett and Marczynski 1971, Marczynski et al. 1971a).

Cholinergic mechanisms in surface positive SPs

The physiological tonus of the cholinergic ARAS component projecting to the thalamus and cortex is necessary for the emergence of RCPV. Doses of scopolamine or atropine, which do not interfere with operant behavior, block the RCPV, which can be restored promptly by administration of physostigmine (Fig. 2 top). The most important aspect of this antimuscarinic blocking action is that the alpha-like bursts associated with RCPV become irregular and "choppy," suggesting that SP production is directly related to the rhythmic hyperpolarizing phasing of neuronal activity. Moreover, the duration of choppy alpha-like activity is not significantly different from control response (Fig. 3). Hence, it can be concluded that antimuscarinics do not block the "primary" effect of reward (or goal achievement), but merely interfere with the "execution" of thalamocortical synchronization and emergence of RCPV (Marczynski 1971).

The phasing theory of neuronal activity explaining alpha mechanisms, which is based on recurrent inhibition (Andersen and Andersson 1968), implies that a certain level of synaptic drive is necessary to initiate the functioning of the recurrent inhibitory circuits. Taking into account the facilitatory cholinergic influences on sensory transmissions at thalamic and cortical levels, one can propose that antimuscarinics, by reducing the cholinergic ARAS influences, lower synaptic drive to a level that is incompatible with normal operation of recurrent inhibitory circuits (Marczynski and Burns 1976). Blockade of alpha activity by antimuscarinics in man (Longo 1966) and blockade of alpha-like activity associated with K-complexes normally triggered by sensory stimuli during sleep onset (Marczynski, this volume) are in agreement with our interpretation of cholinergic mechanisms. Further supporting evidence has been presented elsewhere (Marczynski and Burns 1976; Rick and Marczynski 1976; Marczynski and Karmos, this volume).

Assuming that the proposed interpretation of cholinergic mechanisms is correct, one can make a second assumption regarding the role of synaptic drive in the topographical distribution of positive SPs. Upon completion of task performance, slackening or suppression of the catecholaminergic ARAS component allows inhibitory interneurons to function. Only those thalamocortical projections and corticocortical pathways that received the strongest synaptic drive can be expected to activate recurrent inhibitory circuits promptly. It is, therefore, not surprising that the RCPV in the cat depends on visual input and occurs over primary and secondary visual projections (Marczynski et al. 1971a,b). Similarly, the SPP of Papakostopoulos et al. occurs over the motor and somatosensory cortex, while the DP of Cooper et al. (this volume), which requires intensive visual searching but only a minimal motor response, occurs over the vertex and midline occipital cortex. On the basis of anatomical and electrophysiological evidence (Frigyesi 1972), it is probable that the emergence of SPP depends on activation of motor cortex, as well as strong synaptic drive from the cerebellum, which reaches the cortex via the bracchium conjunctivum and n. ventralis lateralis. Pyramidal neurons of the cortex, in turn, send axons back to n. ventralis lateralis as well as axon collaterals to intracortical inhibitory circuits and to R. The latter, in turn, project inhibitory axons to n. ventralis lateralis (Fig. 4). Immediately after post-performance slackening of the inhibitory ARAS component (catecholaminergic?), both thalamic and intracortical recurrent inhibitory circuits may be activated, resulting in a positive SP and alpha-like EEG oscillations.

Cholinergic activation of the catecholaminergic system

Antimuscarinic drugs block RCPV and alpha activity in humans. Physostigmine restores RCPV and associated alpha-like bursts, but also blocks

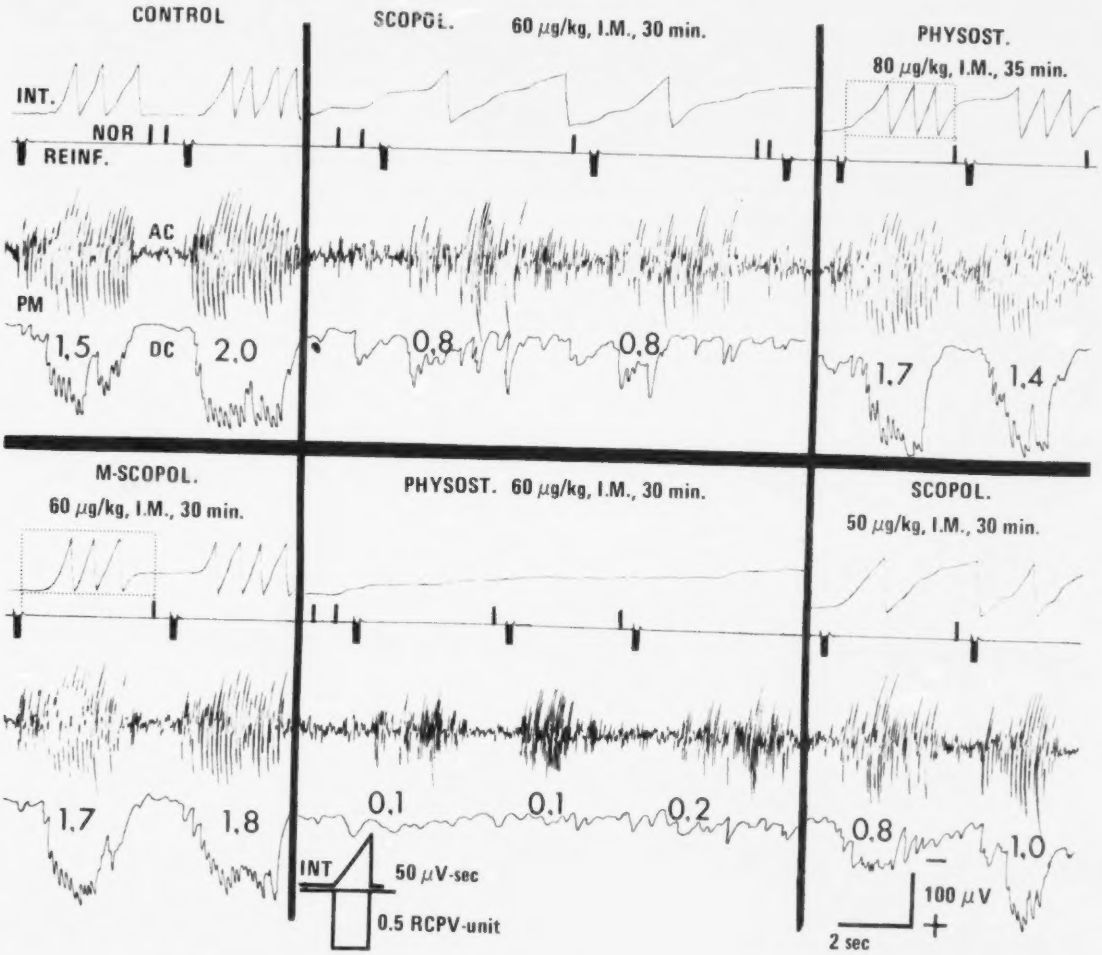

Fig. 2. Top: The effect of scopolamine HBr and physostigmine salicylate on reward-induced EEG synchronization and associated RCPV, recorded over the primary visual cortex (posterior marginal gyrus or PM) with reference to the subjacent white matter. The dc record was filtered out to half-amplitude response at 3 c/sec. This channel is integrated in the first trace (INT) in which two full-scale upward deflections are equal to one unit of RCPV. As marked by dotted lines in the upper right record, only those INT deflections were counted that occurred in the time interval between the reinforced (REINF) and the subsequent rewarded or nonrewarded (NOR) lever press.

Bottom: 48 hours later, the same cat was pretreated with methylscopolamine HBr; physostigmine suppressed the RCPV, which subsequently could be partially restored with scopolamine (From: Marczynski 1971). For further explanation, see the text.

these responses if given to animals whose peripheral muscarinic receptors have been "protected" with methylscopolamine, which does not penetrate through the blood brain barrier (Marczynski 1971). In some instances, as shown in Fig.2 (bottom right), RCPV and alpha-like responses can be restored with scopolamine. Better results have been obtained with chlorpromazine, a drug known to block dopaminergic and adrenergic receptors. Hence, it appears that physostigmine and perhaps other acetylcholinesterase inhibitors, by increasing ACh levels, can activate catecholaminergic systems. Since similar blockade of EEG responses has been observed after systemic administration of nicotine, an effect reversible with chlorpromazine (Marcznski, unpublished), one can postulate that cholinergic activation of catecholaminergic systems results from action on nicotinic receptors. The latter are primarily located in ARAS nuclei at the brainstem level (Kawamura and Domino 1969, Knapp and Domino 1962). The mechanism by which activation of the catecholaminergic system may modulate and block thalamocortical inhibitory and synchronizing circuits has already been discussed.

Clinical implications of impaired neurochemical mechanisms

Catecholaminergic hypothesis of minimal brain dysfunction

Selective attentional deficits are characteristic of children with Minimal Brain Dysfunction (MBD). The role of n. reticularis thalami (R) in gating sensory input and the putative role of catecholaminergic projections in regulating the inhibitory background of this nucleus have been reviewed above. It may be hypothesized that the inhibitory background in R of MBD children is deficient, a condition which is likely to impair the selective gating of sensory input. Moskowitz and Wurtman (1975), for instance, observed that the catecholaminergic system in MBD children seems to be impaired which may lead to uncontrolled functioning of the thalamic gating system. Moreover, MBD children have an unusually low threshold to photic driving which sometimes leads to myoclonus. These children also tend to be hypersensitive

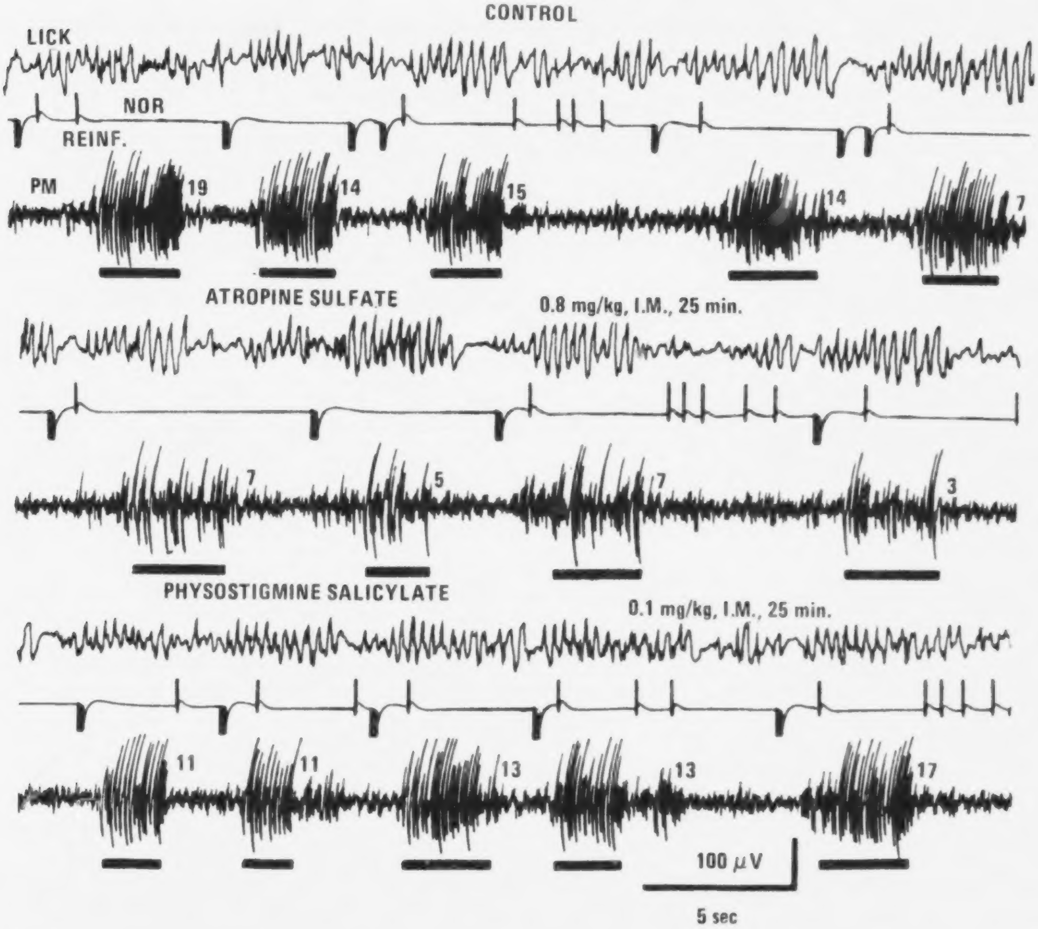

Fig. 3. Comparison of control reward-induced EEG synchronization (top) with that recorded 25 min after administration of atropine sulfate(0.8 mg/kg, i.m.)in the cat trained to press a bar for 1 cc of milk. LICK signals caused by lapping and licking; NOR nonrewarded bar press; REINF rewarded bar press; PM posterior marginal gyrus (with reference to the anterior ectosylvian gyrus). The heavy horizontal bar below each EEG response marks its duration from the first to the last EEG wave that, if measured peak-to-peak, exceeded 100 μV. The numbers after each EEG response tell how many oscillations occurred that exceeded 100μV. Note that the duration of the "choppy" EEG responses is not significantly different from the control. Note also that physostigmine promptly restored the responses (bottom). For further explanation, see the text.

to amphetamine and methylphenidate, as tested by the blocking action of these drugs on EEG photic driving and myoclonus (Shetty 1971). Hypersensitivity to amphetamine implies that catecholaminergic pathways and terminals are damaged. Furthermore, amphetamine and methylphenidate usually ameliorate MBD symptoms.

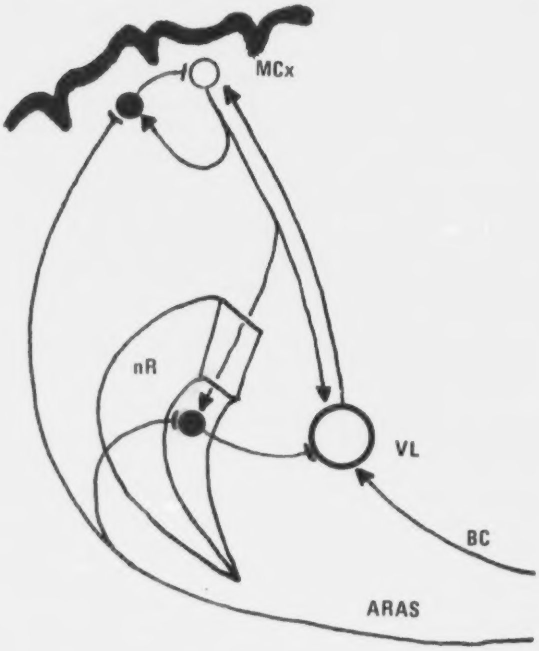

Fig. 4. Pathways most likely responsible for the emergence of the skilled performance positivity (SPP) of Papakostopoulos et al. The arrows and the small bars denote the excitatory and inhibitory (hyperpolarizing) synapses respectively. nR nucleus reticularis thalami; VL n. ventralis lateralis; BC brachium conjunctivum, conveying input to the VL from the cerebellum; MCx motor cortex. Filled circles denote inhibitory neurons. Note that the rhythmic phasing of neuronal activity and the emergence of the SPP are possible only when the inhibitory neurons are released from tonic inhibition exerted by the ARAS (ascending reticular activating system; probably its catecholaminergic component). For further explanations, see the text, (Modified from Frigyesi 1972).

Stamm and his colleagues (personal communication) studied the N1 component of auditory evoked potentials in normal and MBD children. The mean N1 amplitude difference between attend and non-attend conditions was 44 percent for the normal group, but only 14 percent for the MBD group. Karrer and his colleagues (this volume) found that children with cognitive difficulties show an increased surface positive SP over frontal and central cortex prior to and during motor response, both observations support the hypothesis that "sculpturing" of specific excitatory spatio-temporal patterns in R and other pools of thalamic inhibitory neurons is impaired, leading to a low signal-to-noise ratio of input to the cortex (Skinner, this volume).

Cholinergic interpretation of dopaminergic hypothesis of schizophrenia: a new working hypothesis

Relationships among catecholaminergic systems and thalamocortical inhibitory pathways in MBD children may be opposite to those in adults with acute anxiety, schizophrenia, or amphetamine-induced schizophreniform psychosis. That is, increased tonus of catecholaminergic systems is likely to produce tonic inhibition of R and impaired thalamocortical EEG synchronization. This condition is incompatible with effective gating of sensory input and leads thus to a state of confusion. Thalamocortical relationships are discussed further in the "Parsimonious Model of Mammalian Brain" (Marczynski, this volume).

During the last seven years, considerable data have accumulated indicating that a hyperfunction of the DA system and/or increased sensitivity of DA postsynaptic receptors may be responsible for many symptoms of schizophrenia (Meltzer and Stahl 1976). Moreover, Libet and his colleagues (this section) have discovered that DA has a unique and powerful potentiating effect on slow muscarinic EPSPs in sympathetic ganglia. As already mentioned, pyramidal cells of cortical layers IV and V are endowed with "pure" muscarinic receptors. Stimulation of these receptors with ACh triggers EPSPs characterized by slow onset and long duration (Krnjevic 1974). The specificity of this action is indicated by the fact that these EPSPs are associated with an increase in membrane resistance, in contrast to the brisk and short-lasting EPSPs mediated by nicotinic receptors and associated with a sudden drop of membrane resistance.

Following ACh application, neurons in the striatum, a nucleus known to be profusely innervated by DA projections, show typical muscarinic responses comparable to those seen in the cortex. Therefore, they may provide a clue regarding the possible interaction between DA and ACh systems. Indirect evidence for such a heterosynaptic interaction at postsynaptic sites comes from intracellular recording of striatal neurons. Electrical stimulation of the substantia nigra activates DA projections to the striatum and causes release of ACh in this structure (Portig and Vogt 1969). This dual effect is probably caused by the proximity of the ARAS cholinergic component described by Shute and Lewis (1967). Electron microscopic study of DA terminals in the striatum shows that DA is likely to be released through narrow pits directly into relatively large extracellular spaces, allowing for diffusion of the transmitter away from the terminal (Tennyson et al. 1974). These morphological characteristics imply that a heterosynaptic interaction at postsynaptic sites is possible, an assumption supported by an intracellular study of striatal neurons by Hull et al. (1970). These investigators found that a single volley of electrical stimuli applied to substantia nigra, or its close vicinity, produced in most neurons a short-lasting hyperpolarization (DA effect ?), followed by an exaggerated depolarization lasting 30 to 40 seconds. This phenomenon, which resembles the paroxysmal depolarization shift of neurons in epileptic foci, was not observed in other structures.

Although the information concerning the intricate relationship between DA and ACh terminals in the cortex is not yet available, the possibility of interaction between these two neurotransmitters at muscarinic receptor sites in schizophrenics should be seriously considered as a working hypothesis because all the necessary elements are present in the cortex, including the DA receptor, i.e., DA-sensitive adenylate cyclase (Bockaert et al. 1977). Considerable evidence supporting this hypothesis is already available. First, there is little doubt that increased tonus of the DA system plays a crucial role in the emergence of most schizophrenic symptoms (Meltzer and Stahl 1976). Secondly, several electrophysiological observations indicate that exaggerated depolarization of cortical neurons and their apical dendrites may be associated with schizophrenic symptoms. For instance, schizophrenics show considerable impairment of amplitude recovery of auditory, somesthetic, and visual evoked potentials if the stimuli are presented at short intervals (Shagass 1976). Thirdly, acute or chronic schizophrenics with florid symptoms show significantly lower CNV amplitude than normal adults (Dongier 1973).

Later components of cortical evoked potentials are produced by postsynaptic potentials and their electrotonic spread to apical dendrites (Creutzfeldt et al. 1969). Tonic depolarization of apical dendrites by cathodal current (Purpura 1967) or by application of ACh (Sigg et al. 1965) reduces the slow negative component of evoked potentials. It is likely that CNV amplitude is similarly diminished relative to background depolarization of apical dendrites during hyperarousal. Hence, modifications of the CNV paradigm, making it more demanding—e.g., by introducing distracting stimuli—lead to reduction of CNV amplitude (Tecce and Cole 1976). Administration of amphetamine to experimental animals reduces negative SPs over frontal cortex elicited by conditional auditory stimuli, an effect that can be reversed by haloperidol or barbiturates (Pirch, this section). Likewise, the administration of fluphenazine to schizophrenics with florid symptoms considerably enhances CNV amplitude and improves the clinical picture (Tecce and Cole 1976). On the other hand, when no drug-induced or disease-related hyperarousal is present, one would expect a reduction of CNV amplitude to parallel the slackening of ARAS tonus or blockade of postsynaptic receptors. Indeed, Thompson et al. (this section) found that atropine or a DA antagonist, metoclopramide, decreased CNV amplitude in normal volunteers. In conclusion, the above physiological and pharmacological considerations support the theory that CNV amplitude is monotonically related to selective attention, but nonlinearly related (inverted U) to increasing ARAS tonus and arousal level (Tecce and Cole 1976).

Finally, the prolongation of the spiral aftereffect (SAE) described by Herrington and Claridge (1965) appears to represent one of the most characteristic phenomena associated with schizophrenic symptoms (Abraham and McCallum 1973). A recent study of SAE in schizophrenics and controls revealed that its duration faithfully reflects the actual clinical state as judged by Schneider's first-rank symptoms. This correlation was present even when amplitude reduction or prolongation of the CNV was marginal or absent (Abraham and McCallum, personal communication).

Little is known about the neurophysiological basis of SAE. This phenomenon may, however, be related to transient entrainment of neuronal circuits involved in motion detection. A classical example of such entrainment is the "waterfall effect." If one stares at a waterfall and then looks away, a part of the background corresponding to the size of the waterfall appears to move upward, while the rest of the landscape remains stable. This illusion is not caused by eye movement, but by entrainment of neuronal circuits most likely involving edge and/or motion detector cells in the striate cortex.

It is quite probable that SAE duration is regulated by a cholinergic mechanism of the muscarinic type. Neurons which normally discharge briefly (0.5 to 1.0 sec) in response to a sensory volley, respond to the same input after iontophoretic application of ACh with a continuous burst of action potentials lasting 10 to 20 sec (Krnjevic 1974). Thus, a primary role of the cholinergic ARAS component projecting to the cortex is to amplify in time the transient sensory input, a process believed to be necessary for the emergence of conscious experience (Libet 1965, Krnjevic 1974). Hence, prolonged SAE in schizophrenics is likely to reflect a pathological potentiation of the normal function of the cholinergic ARAS component, an action that may be tentatively ascribed to DA modulation of postsynaptic muscarinic receptors.

Summary

The enormous complexity of dynamic interactions among neuronal ensembles and chemical transmitters or modulators necessitates a multidisciplinary approach to the study of brain function. This review attempts to integrate many anatomical, electrophysiological, and pharmacological aspects of the genesis and functional significance of EEG patterns, evoked potentials, and slow potentials. Evidence is presented that EEG desynchronization and slow negative potentials are mediated by a concerted action of the cholinergic and catecholaminergic ARAS components. The cholinergic component depolarizes neuronal dendrites, reduces the firing threshold of large populations of neurons in specific thalamic nuclei and cortex, and prolongs their discharge to incoming volleys. Simultaneously, the catecholaminergic ARAS component appears to block the function of GABA-ergic recurrent and/or feedforward inhibitory circuits responsible for hyperpolarization of large populations of neurons. Conversely, bursts of alpha-like EEG patterns, surface positive SPs and most positive SPs in the specific thalamic nuclei seem to result from slackening in the tonus of catecholaminergic projections, thus allowing the function of GABA-ergic hyperpolarizing circuits, the emergence of alpha-like EEG patterns, and positive SPs.

Antimuscarinic drugs (atropine or scopolamine) block at the thalamocortical level not only the normal cholinergic facilitation (amplification in time) of sensory input, the negative SPs and EEG desynchronization, but also abolish opposite phenomena, such as the bursts of EEG alpha-like patterns and positive SPs in specific thalamic nuclei and cortex. These dual and seemingly contradictory actions of these drugs can be accounted for by two assumptions based on experimental results: (1) the functioning of the recurrent inhibitory GABA-ergic circuits depends on a certain level of excitatory synaptic pressure and its physiological amplification by the cholinergic ARAS component; and (2) this pressure can either be converted into a desynchronized EEG pattern and negative SPs or into a hypersynchronized EEG alpha-like pattern and positive SPs, depending upon the functional state and "readiness" of the GABA-ergic circuits. If the latter are tonically inhibited by the ARAS (catecholaminergic projections?) e.g. during arousal, the excitatory synaptic pressure can only result in EEG desynchronization and negative SPs in specific thalamic nuclei and cortex. However, if the GABA-ergic system, e.g. during relaxed wakefulness, is released from tonic inhibition (slackening of the catecholaminergic ARAS component?), the excitatory synaptic pressure in specific thalamic nuclei and cortex can be readily converted into hyperpolarizing inhibition, bursts of high voltage alpha activity and positive SPs in specific thalamic nuclei and cortex.

The issues discussed here have several clinical implications. For instance, it appears that a moderate (catecholaminergically mediated) inhibitory background in reticularis thalami (reflected as a positive SP in this structure) is necessary for the gating of sensory input by this nucleus. This function is likely to be impaired in children with MBD. On the other hand, an excessive hyperpolarizing blockade of this nucleus by catecholaminergic projections could render it nonresponsive to corticofugal modulation and cause an overload of sensory input and confusion—characteristic symptoms of schizophrenia. To account for changes in SPs in schizophrenic patients, heterosynaptic interaction between dopaminergic and cholinergic systems is postulated.

REWARD CONTINGENT POSITIVE VARIATION (RCPV) AND PATTERNS OF NEURONAL ACTIVITY IN THE VISUAL CORTEX OF THE CAT

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The relationship between the firing patterns of cortical and subcortical neurons and slow potentials (SP) has been studied by several investigators. Fromm and Bond (1964) found that in the encéphalé isolé cat preparation, cortical neurons in the visual projections fire more frequently during surface positive EEG waves and cease firing during negative waves. These relationships were reversed, however, when the visual cortex became more negative with respect to the frontal sinus. Rebert (1973b) found that flash stimuli produce in the lateral geniculate body a slow negative SP associated with increased neuronal firing. In the chronic cat preparation, under conditions of nonoperant training, Rowland (1974) found that surface negative SPs over the visual cortex were associated with increased multiple unit activity.

Clemente et al. (1964) observed postreinforcement synchronization (PRS) of EEG in cats trained to press a lever for milk reward. Marczynski et al. (1969, 1971a) have shown that PRS (7 to 9 c/sec) is always associated with an epicortical SP which has been designated reward contingent positive variation (RCPV). This phenomenon, like PRS (Sterman and Wyrwicka 1967), depends on the quality and desirability of reward. The PRS-RCPV responses are topographically restricted to the primary and secondary visual projections and a part of the association cortex (the posterior marginal and the suprasylvian gyri). The RCPV usually outlasts the PRS burst by 1 to 2 sec (Marczynski et al. 1971a, Rick and Marczynski 1976).

In the present study, the relationship between patterns of single-unit activity and the PRS-RCPV phenomenon was investigated. Since PRS-RCPV responses depend on unpatterned light input, even in cats trained in the dark (Marczynski et al. 1971b, Rick and Marczynski 1976), the effect of ambient light was also tested.

Methods

Eight adult cats were trained to press a lever for 0.8 ml of milk reward. Ag/AgCl electrodes were implanted epidurally over the posterior marginal (PM) and anterior ectosylvian gyri in three cats under pentobarbital anesthesia. Since the latter electrodes were relatively "neutral" during PRS-RCPV responses (Marczynski et al. 1971a), they served as reference. In two other cats, the reference electrode was placed in the white matter of the PM gyrus approximately 6 mm below the surface and 3 mm lateral from the epidural electrode. The subcortical reference consisted of a 0.5 mm Ag/AgCl pellet, enclosed in a glass tube, which was closed with agar. In the remaining three cats, no dc recording was attempted: PRS and unit activity were monitored using standard epidural stainless steel electrodes in the cats. In all eight cats, single- or multiple-unit recordings from PM gyrus were obtained by means of bundles of "floating" platinum-iridium or stainless steel wires, 15 to 35μm in diameter, insulated except at the tips which were cut with scissors. The bundles of wires, stiffened with sucrose solution, were implanted through a guide cannula, which was tangentially oriented and made out of a polyethylene or stainless steel tubing 0.5 mm in diameter. The tip of the cannula was cut at approximately a 20° angle, and its orifice was provided with a l-mm rim. Through a small opening in the dura, the rim was placed above the pia mater, and the cannula was fixed to the skull. Wires and epidural electrodes (including the white matter reference) were connected to separate miniature sockets. Unit activity was recorded with a miniature high-input impedence preamplifier (Sherry et al. 1975), with wide frequency band responsiveness (1.0 to 1.5 Hz). Notch filters and Grass 7-P511 amplifiers permitted simultaneous recording of unit activity and slow wave ECoG patterns from the electrode tip. Of 52 "floating" wires, 10 yielded good single or multiple unit recording for 2 to 9 days in unrestrained animals. Data were stored on magnetic tape. An amplitude discriminator was used for separation of multiple unit activity. Frequency histograms of unit firing were obtained with a Computer of Average Transients Model 1200 and displayed by means of an X-Y plotter.

Results

All eight cats showed typical PRS responses in the presence of ambient light. In the dark, consummatory responses were not associated with any significant changes in ECoG or SP. In all cats implanted with Ag/AgCl electrodes, PRS was always associated with a typical RCPV, as shown in Fig. 1A (S: surface lead referred to white matter). Steep negative waves of 7 to 9 c/sec recorded with the intracortical microelectrode (D) were always in phase with bursts of unit activity. During a fully developed PRS response, these intracortical negative waves were abruptly terminated by much longer duration (approximately 100 to 130 msec) positive waves. Surface negative waves were, in most instances, approximately 20 to 35 msec out of phase with respect to intracortical ones. The duration of surface positive waves was comparable to that of intracortical waves.

In the presence of light, all 10 successfully studied neurons showed markedly reduced firing rate during consummatory responses associated with the PRS-RCPV phenomenon as compared to the time period immediately prior to, during, or immediately after the lever press. As shown in Fig. 1B (L: frequency histograms obtained in the light), the higher amplitude unit H and the small amplitude unit S were maximally suppressed during the time period between 2 and 4 sec after reinforcement (R), i.e., during the consummatory responses and the occurrence of PRS-RCPV. Since cats performed on a 6-sec fixed interval reinforcement schedule, the histograms encompassed approximately two consummatory responses and, therefore, were almost symmetrical on both sides of reinforcement.

Basically, two types of units were encountered: one type showed no significant change in firing rate in the dark (D), i.e., when PRS-RCPV responses were suppressed, but showed strong post-reinforcement inhibition in the light (the histograms S-D and S-L, respectively). The second type of unit, illustrated by neuron H, showed increased firing rate approximately

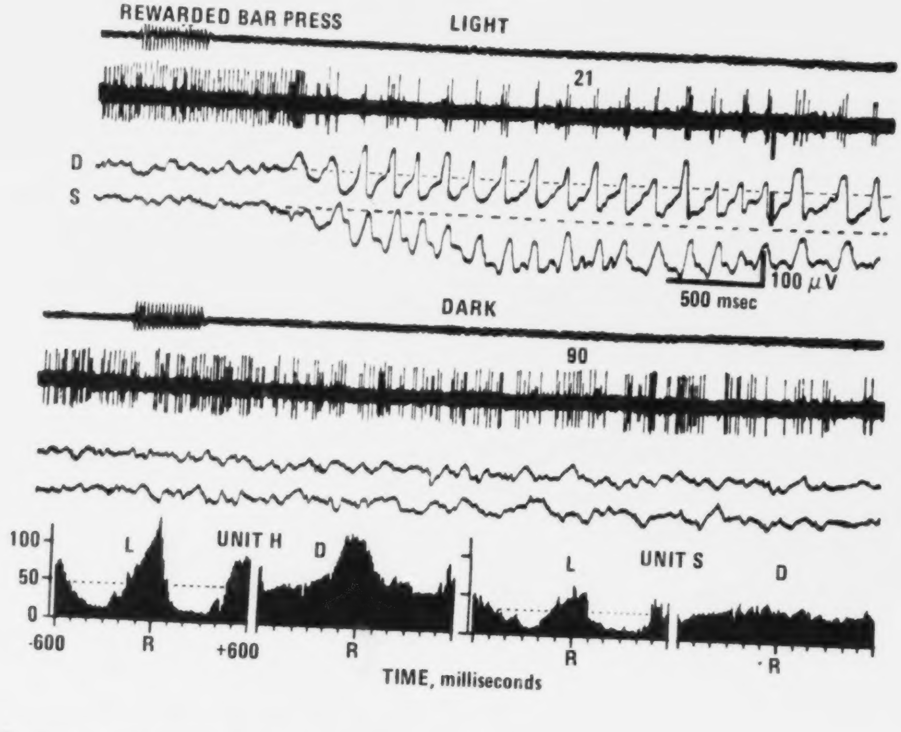

Fig. 1A: Patterns of unit activity in the visual cortex, simultaneously recorded intracortical ECoG from the tip of the same electrode (D) and surface ECoG(S) during lever pressing performance for 0.8 ml of milk reward. The reference electrode placed in the white matter approximately 3 mm laterally from the intracortical and epicortical electrodes. B: frequency histograms for higher amplitude (H) and smaller amplitude (S) units during performance of the cat in the presence of light (L) and in the dark (D). Numbers above the unit channel show discharges for unit H after reinforcement in light and dark. Bin width in histograms: 100 msec. Each histogram represents 10 rewarded (R) lever presses.

1.5 sec prior to, during, and 1.5 sec after reinforcement, both in the presence and absence of light (histograms H-L and H-D, respectively). Both types of units, however, were strongly inhibited during consummatory responses in the light i.e., during the occurrence of PRS-RCPV. As shown by the dashed line in L histograms, firing rate during PRS-RCPV reached markedly lower levels than the average firing rate observed during a relaxed state after satiation.

During sleep onset after satiation, ECoG and SP patterns were indistinguishable from PRS-RCPV responses. In contrast to operant behavior, however, the characteristic 7- to 9- c/sec bursts of discharges and an overall decreased firing rate were observed in all units both in the dark and light.

Discussion

The PRS phenomenon and associated suppression of unit activity in the cortex seem to represent a typical example of phasing of neuronal discharges based on recurrent inhibition as postulated for thalamocortical relationships by Andersen and Andersson (1968). The phasing theory that explains recruitment of larger populations of neurons into alpha-like discharges implies that a certain level of synaptic pressure is necessary to initiate and drive the phasing circuitry. Hence, neurons that show sustained on-responses to light (Corazza et al. 1971, Hom 1965, Jung et al. 1963, MacLean et al. 1968) may be the main source of "electromotive energy" that could initiate the phasing mechanism during the brief (but apparently strong) reward-induced suppression of the brainstem reticular activating system (Marczynski 1972a, Marczynski and Burns 1976). This suggestion is supported by the observation that, in the dark, single and relatively weak electrical stimuli applied to the optic nerve during consummatory responses trigger in a stimulus-bound manner typical PRS-RCPV responses whose patterns and topographical distribution are virtually identical with those of spontaneous responses in the presence of ambient light (Rick and Marczynski 1976). The specificity of the effect of this "noisy" electrical stimulation was demonstrated by the fact that the same, or even stronger, stimuli applied during other behavioral states, such as nonrewarded lever pressing or relaxed wakefulness after satiation, produced no effect. In conjunction with previous data on the role of unpatterned light input in the emergence of PRS-RCPV responses (Marczynski et al. 1971b), it can be concluded that "noisy" photic input is effectively utilized in reward-induced inhibition of neuronal activity in the feline visual cortex, therefore, in the broader sense, in the integration of input associated with consummatory responses.

The occurrence of the epicortical positive shift, i.e., RCPV in association with the PRS bursts, can be interpreted as resulting from a phasic tendency toward hyperpolarizing inhibition of larger populations of neurons in the cortex and the electrotonic spread of IPSPs to apical dendrites, which is reflected as surface positivity (Creutzfeldt et al. 1969). A more detailed analysis of the PRS-RCPV phenomenon, pathways involved, pharmacology, and physiological significance has been presented elsewhere (Marczynski and Burns 1976).

Acknowledgment

The help of Dr. C. J. Sherry in the early phase of this study is appreciated.

ACQUISITION OF SUSTAINED POTENTIALS DISSOCIATED FROM MASSED ACTION POTENTIALS IN TEMPORAL CONDITIONING

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The CNV may be seen as a sustained, nonoscillatory field potential of the shortest end of the spectrum of sustained electrophysiologic durations. This spectrum extends from a half second up to several minutes in duration, as can be shown by conditioning experiments (Rowland and Goldstone 1963, Sheafor and Rowland 1974). Also, the potassium-induced glial depolarization mechanism of genesis of sustained potential fields may be seen as a possible temporal integrating or timebinding mechanism, although, to my knowledge, no direct experimental demonstration of such a role has yet been offered.

Interest in such a role is enhanced by the failure to demonstrate actual circulating or reverberatory iterated fast-decaying transients such as action potentials, short postsynaptic potentials, or wave trains (oscillating field potentials) to account for identifiable electrophysiologic states sustained for more than a half second. The only known alternative is for the action of transients to be transformed by other cell parts or systems to dynamics having much slower decay-time constants, thereby producing temporal summation.

In order better to understand the relation of nontimebinding transients (action potentials) to the sustained field potentials reflecting the temporal integration of generators of slower decay, we (Rowland and Dines 1973) developed small hybrid macroelectrodes and circuitry for simultaneously registering an artificial integration of massed action potentials (integrated mass units, or IMU), the conventional oscillatory field potential patterns (electrocorticogram, or ECoG), and sustained slow potentials (SP).

Many examples of the expected association of IMU increments with ECoG and SP activation were observed in cortex (Rowland and Dines 1973), as described by Rebert (1973b) for the lateral geniculate. Also IMU decrements were observed with ECoG synchrony and clear mass unit bursting in phase with individual high-voltage, low-frequency waves of spindle activity.

By serendipity, in relation to studies of the IMU-SP relation occurring with food rewards, the appearance of marked anticipatory SPs without associated IMU changes was encountered (Rowland 1974). The same system continued to show the associated IMP-SP relations formerly seen in reaction to stimuli or association with an emitted potential, the lambda wave. The reactive, associated IMU-SP relation is identified in this paper as SP-1, and the proactive (anticipatory) dissociated relation (SP present in the absence of IMU change) as SP-2. Fig. 1, taken from Sheafor and Rowland (1974), shows the replacement of SP-1 in the naive animal by SP-2 after 3 weeks of training. Essential to the demonstration of SP-2 is a state called quiet expectancy. This was developed in the cats in this study by their being trained to restraint in a stock that permitted them to sit comfortably. They received food directly into the mouth every 4 min. They had 5 sec of tone (R) prior to each reinforcement, and 8-cm^3 feeding. The same tone was repeated 2 min later at the middle of each 4-min interval but not reinforced (N) in a program called single alternation (SA). The cat's cortical SP developed a clear 2-min phase of anticipation of forthcoming reinforcement while the animal remained behaviorally quiet. If it spontaneously moved, a transient SP-1 would appear superimposed on the sustained ramp of the SP-2.

No evidence was observed in the IMU record of the graded expectancy or proactive response prior to either N or R tone, whereas the SP was maximally positive or least negative prior to the N tone and gradually and regularly became maximally negative prior to the tone.

Fig. 1 shows, in the course of acquisition, the development of a proactive SP-2 through an initial phase at 11 days, interpretable as related to the animal's generalizing the N and R tones. The N tone produces marked change in the IMU and SP. Subsequently (day 14), both of these disappear, suggesting that the animal has begun to discriminate the difference at the same time as the sustained ramp over the second half of the 4-min interreinforcement interval emerges. Since N and R tones are the same, the animals have only their capability of monitoring the lapse of time (independently of direct cueing) to enable the discrimination between forthcoming reinforcement and nonreinforcement. This discrimination is not seen just prior to the tones in the IMU record (Fig. 2). It is seen clearly in the SP-2 pattern. If further tests support the interpretation that a true dissociation between the two variables exists, the conclusion follows that the SP-2 generating mechanism has access to stored experience independently of the action potential generating mechanisms. The proactive response can only develop in the context of temporal oreintation arising from the relatively remote memory of prior days of training and the recent memory of when the last reinforcement occurred.

Nothing is known from direct experiments about the mechanisms of genesis of the proactive SP-2. It appears to be some other mechanism than the release of potassium generated by mass action potential activity inducing the presumed glial depolarization postulated for reactive SP-1 genesis (Ranson and Goldring 1973b). A more extensive consideration of possible mechanisms such as synaptic potentials operating independently of action potentials, intracellular electrotonus, etc., is presented in Sheafor and Rowland (1974). A further candidate mechanism to be considered is the diffuse release of a neurotransmitter by the "varicosities" of axons that originate in cells of median raphe or other brain stem nuclei.

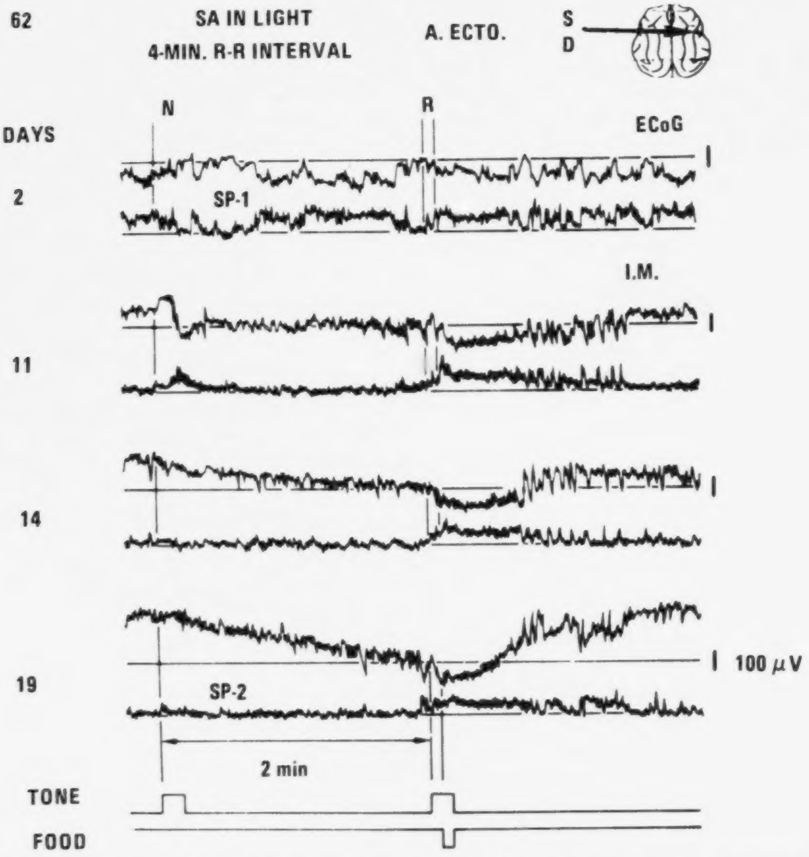

Fig. 1. Representative pairs of ECoG-IMU tracings for individual trials taken from days indicated illustrate the SP-IMU relationships observed during SA training in Cat 62. Close SP-IMU association (SP-1) was characteristic during early acquisition (Day 2) and was obtained with R and during post-R intervals throughout training (right half of the figure). As the pre-R (N to R) negative SP was acquired (left half of the figure), it became increasingly dissociated from the IMU measure (SP-2). Multiple unit integrator output is filtered from dc to half-amplitude frequency response at 1.5 Hz in all figures except Fig. 3. Negativity is down for Fig. 1-3.

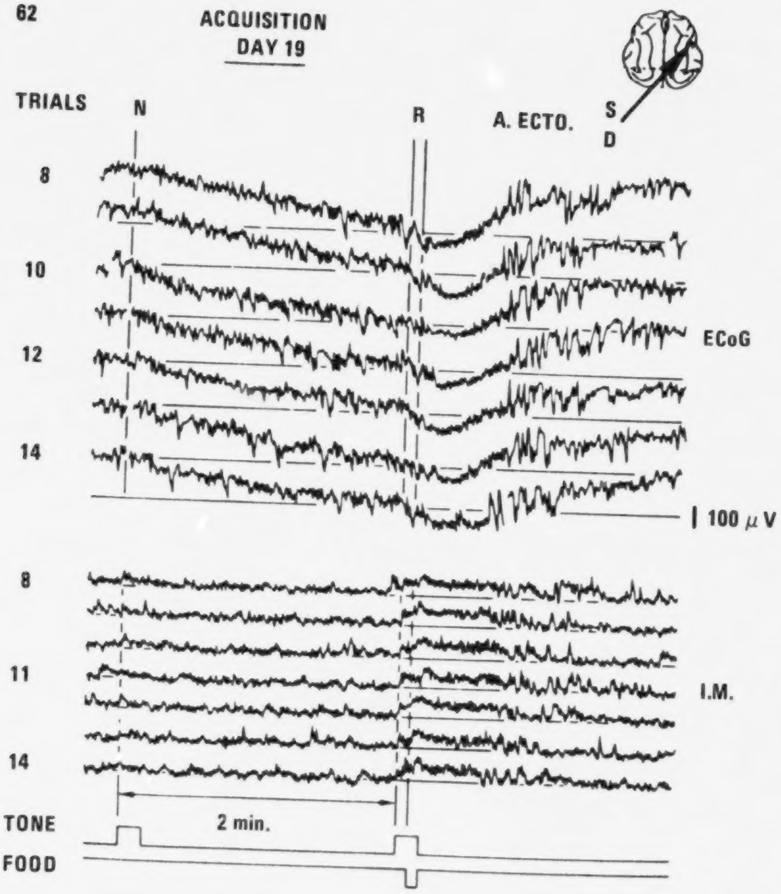

Fig. 2. Representative ECoG tracings of seven consecutive trials (28-min continuous recording) illustrate reliability of the SP pattern (top) acquired in the SA schedule in Cat 62. In relation to corresponding IMU tracings (bottom), reliability of SP-IMU dissociation (SP-2) during the pre-R (N to R) interval and SP-IMU association during the post-R (R to N) interval is demonstrated. IMU tracings also show incrementing in CS-UCS interval of the R trials but little or no change to the same tone in the N trials.

Slope and duration of SP-2 has been shown to depend on the interval between reinforcements. Also, it is found to be relatively independent of the N and R tones. The graded sustained potential is also of interest as a possible alternative to an oscillator system as an internal clock, but it remains to be shown that the SP itself is not dependent on underlying oscillators.

The above description pertains to SPs of long duration as dependent variables. Their roles as an independent variable have only been indirectly implied in the behavioral studies of Roy Anderson carried out in our laboratory. Anticipatory SP shifts recorded without benefit of associated observation of IMU were seen to appear in cortices of rats on both fixed-interval and fixed-ratio responding. Again, the slopes of the expectant portion of the interval were proportional to the time intervals governing the animal's behavior. To my knowledge, there has been no specific test of whether the distribution of SP levels reached just prior to a timed lever press correlates with the distribution of times of responding in a specific timing task in animals; however, Anderson observed a statistical proportionality between the degree of anticipatory cortical SP developed and the proportion of lever presses produced in three fixed-interval programs (Fig. 3). A constant intersection point for the

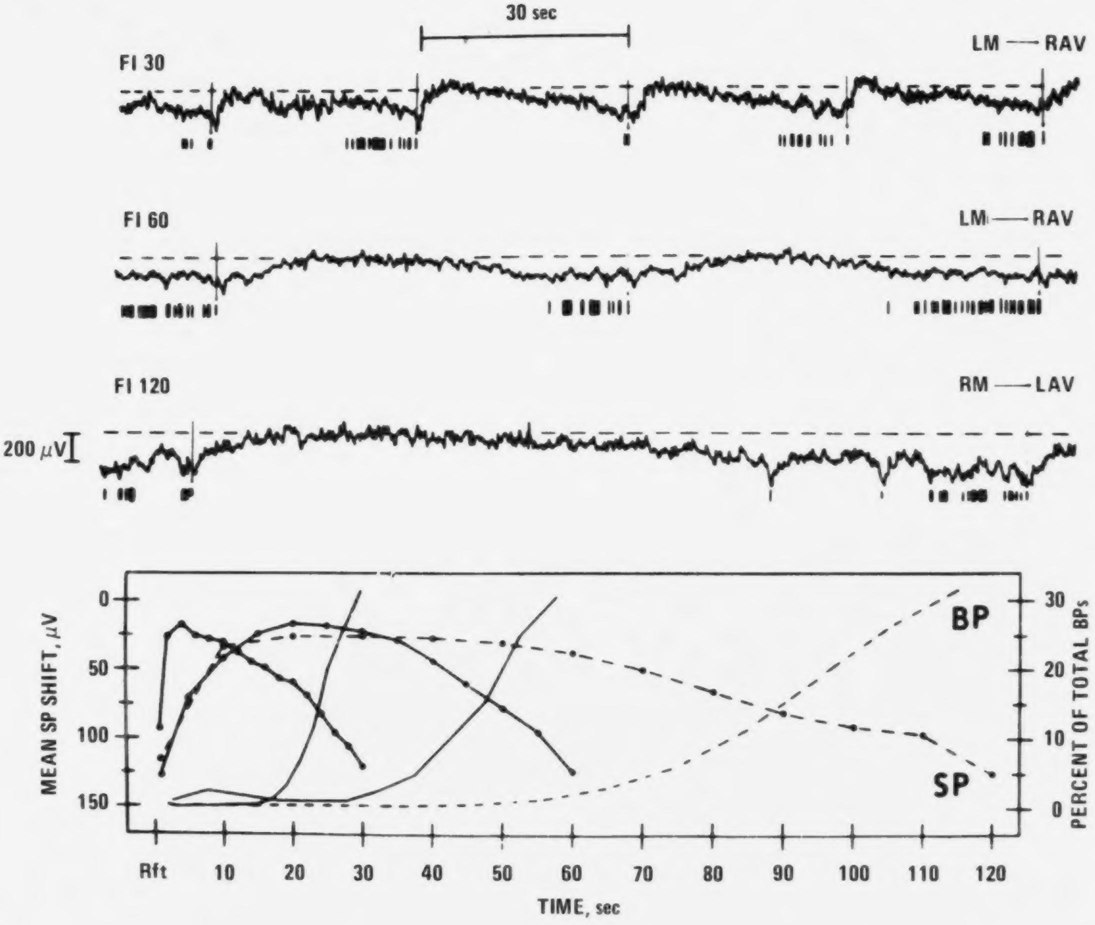

Fig. 3. Upper half, patterns of SP shifting recorded during the fixed interval (FI) training with intervals of 30 sec (top), 1 min (middle), and 2 min (bottom). Records from three different rats. In each record, bar pressing is anticipated and accompanied by a sustained SP shift. Electrode placements are given at the right (LM-RAV = left motor with right anterior visual reference; RM-LAV = right motor with left anterior visual reference). Bar presses are shown as vertical marks below the corresponding record. Pellet reinforcement occurs at the longer vertical line at the end of lever pressing. Lower half, mean amplitude of shift (downward curving arcs) and percent of total bar presses (BP, upward curving graphs) as a function of time during FI performance. Note the direct correspondence between the slope of the shift (activation) gradient and the distribution of bar presses with intersections of curves falling near a constant SP voltage (about 50% of maximum) and percentage of bar presses (15%) for all three intervals. Number of subjects: 5 for FI 30-sec performance, 12 for FI 1-min performance, and 11 for FI 2-min performance. Data points were determined by averaging 120 reinforced intervals per rat. (From Rowland 1974, attributed to Roy Anderson.)

three proportionalities was found—that is, on the average, 50% of the SP was attained at the time the animals had emitted, on the average, 15% of the total lever presses per interval, for whichever schedule they were trained to.

The long sustained SP shifts of the type dealt with here differ from other event-related potential studies in that they are oriented to time intervals between events, and are involved with graded state changes anticipating reinforcements. They are thus construed as endogenously proactive rather than simply reactive to environmental stimuli, as is the case with more conventional physiological analysis. They differ from the readiness potential in being relatively independent of the specific behaviors being controlled and are seen in quiescent subjects.

EVENTS CONTINGENT UPON CORTICAL POTENTIALS CAN LEAD TO RAPID LEARNING

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Research reported in this volume deals primarily with ERP parameters as functions of experimentally controlled conditions–i.e., these potentials are considered as dependent variables. In the present investigation, a different experimental strategy was employed: the occurrence of specified electrocortical events as dependent variables was utilized for training monkeys on a spatial delayed response (DR) task. The start of each DR trial was made contingent upon computer-detection of an endogenous cortical potential of predetermined magnitude. The dependent variable–the rate of task acquisition–was then assessed as a function of the characteristics of the pretrial contingency.

In previous research (Stamm and Rosen 1972), macropotentials were recorded from several cortical areas during performance of a DR task. The averaged recordings delineated several distinct surface-negative slow potential (SP) shifts during the course of a trial, one of which occurred in prefrontal cortex toward the end of cue presentation and the start of the intratrial delay. This shift seemed important in relation to task performance because its magnitude was significantly correlated with the level of correct responses, but not with the duration of either the cue presentation or the delay. The physiological significance of this SP shift is suggested by the finding that prefrontal units increase their firing during corresponding epochs of the DR trial (Fuster 1973, Niki 1974).

Investigations of the functional role of prefrontal cortex in humans and monkeys have provided evidence for its implication in the regulation of attentive processes (Fuster 1973, Picton and Hillyard 1974, Pribram and Luria 1973). In accordance with this view, the occurrence of prefrontal SP shifts and unit activation during DR performance may be considered as an expression of a heightened attentive state. Attention is especially important during cue presentation when the monkey must recognize the significance of the location of the cue in order to program a subsequent instrumental response. This interpretation may be relevant to the general observation that monkeys normally learn the DR task very slowly, requiring many hundreds of trials to attain criterion performance. Slow acquisition may be a consequence of training with constant intertrial intervals because the spatial cue is then often presented while the monkey is inattentive. Conversely, if cues are presented during periods when monkeys are in a state of high attention, more rapid task acquisition should result.

This hypothesis was examined by using the monkey's endogenous prefrontal surface-negative SP shift for starting the DR trial. Verification that such a contingency would lead to rapid task acquisition required control of other factors that could account for any observed effect. Since enhanced acquisition rates could result from generalized cortical activation, monkeys were also trained with pre-cue negative SP shifts from precentral cortex. In addition, animal training procedures have shown that the requirement of a preparatory response for trial initiation, such as the pressing of a "readiness" lever, leads to more effective and consistent task performance (e.g., Niki 1974). Therefore, monkeys were also trained under conditions of trial initiation contingent upon the occurrence of a behavioral response (lateral eye deviations). This ocular movement was selected because it is relatively simple, clearly identifiable, and has been found concomitant with operantly conditioned prefrontal SP shifts (Rosen et al. 1974).

Methods

Methods have been further detailed elsewhere (Sandrew et al. 1977). A total of 13 stumptail monkeys *(Macaca speciosa)* were trained. Under sodium pentabarbital anesthesia, pairs of Ag/AgCl nonpolarizable electrodes (Rowland 1968) were chronically implanted bilaterally in prefrontal, precentral, and occipital cortex with one electrode of each pair on the cortical surface and the other in subjacent white matter. Prefrontal surface electrodes were situated on cortex in the depth of the posterior third of the principal sulcus. Miniature epoxy resin electrodes were cemented to the bony orbit to record electrooculograms (EOGs).

During testing the monkey was placed in a restraining chair, and its left arm was attached by wrist cuff to the shelf of the chair. The chair was in front of a vertical panel that contained two circular display windows, situated at the monkey's eye level, with 12 cm between centers. This separation corresponded approximately to a 36° angle from the monkey's nose. Each window served as both projection surface for the stimuli and manipulandum for the monkey's response. A plastic food cup was mounted at the center, below the windows. The DR trial started with cue presentation, a 1-sec white illumination of either the left or right window, followed by a blackout period–the intratrial delay. Both windows were then illuminated with blue light, and the monkey's press on either window started another blackout period, the intertrial interval (ITI). A correct response (on the cued panel) was rewarded with delivery of a sucrose pellet (45 mg) to the food cup. Each testing session consisted of 98 trials, with a pseudo-random sequence for left and right cue presentation.

During testing sessions, the monkey was connected by shielded cables to dc preamplifiers of a Grass Polygraph. Transcortical electrocorticograms (ECoGs) and horizontal EOGs were recorded on seven-channel magnetic tape. Selected channels were monitored on-line by a PDP-12A computer programmed to detect SP or EOG events that fell within a defined voltage change over time. Upon detecting a criterion event, the program initiated cue presentation. ECoG, EOG, behavioral data, and trigger pulses were stored on digital tape.

Prior to surgery all monkeys were adapted to the testing situation and trained with 8-sec ITIs on 0-sec DR until they made 88 correct responses in one session. Following surgery, each monkey was assigned to one of four training groups (Table 1): (1) Group FSP (n=4)–cue presentation contingent upon computer detection of a left prefrontal surface-negative SP shift of 50-100 μV and 2.5-sec duration; (2) Group MSP (n=2)–cue presentation contingent upon detection of a SP shift of the same parameters from left precentral cortex; (3) Group LEM (n=2)–cue presentation contingent upon detection of an EOG voltage change that corresponded to an eye movement to the right of approximately 40° during a 1.5-sec epoch; and (4) Group YC (n=5)–no pre-cue requirements. Each YC monkey was yoked for ITIs to one in another group (three to FSP monkeys and one each to an MSP and an LEM). This was accomplished by recording ITIs for each session and programming these for the corresponding session with the yoked-control animal.

Each monkey was first trained under the contingent (on-line) condition on 2-sec DR until 90% correct response was reached in one session. In order to assess performance transfer to noncontingent (off-line) conditions, each monkey was then tested (one or two sessions) with constant ITIs equal to the mean ITI during the previous on-line session. If performance fell below criterion, on-line testing was repeated. This procedure was repeated with successive delays of 4, 8, and 12 sec. The final testing phase was designed for more direct evaluation of the monkey's attentive functions by reducing the duration of cue presentation. Monkeys were retrained under on-line conditions on 12-sec DR and 1-sec cues. During the subsequent two sessions, trials were programmed in a random sequence for cue durations of 0.5, 0.2, and 0.1 sec.

Results

Averaged ECoGs and EOGs for an FSP and an LEM monkey are presented in Fig. 1. Recordings for every FSP monkey showed that the large pre-cue negative SP shift was preceded by a smaller positive wave that started about 4 sec before cue onset (Fig. 1A). Criterion SP shifts were localized in left prefrontal cortex; no concomitant SP events were observed at right prefrontal, precentral, or occipital electrode locations. ECoG recordings for MSP monkeys indicate a similar sequence of pre-cue SP shifts, localized to the left precentral area. EOGs for LEM monkeys (Fig. 1B) show that the large pre-cue rightward eye deviation was preceded by a smaller deviation to the left and was followed by return toward baseline level. For trials with left cues, these monkeys attained maximal leftward eye deviations at approximately 0.5 sec after cue onset, and their EOGs indicated a subsequent drift to baseline levels. Comparisons of ECoGs and EOGs during the pre-cue period indicated no systematic relationships between SP shifts and lateral eye deviations. The pre-criterion leftward eye deviation seen in Fig. 1A was not found for the other FSP monkeys. During testing under off-line (constant ITI) conditions, pre-cue ECoG and EOG traces remained near baseline levels for all monkeys, including YCs.

Behavioral results (Table 1) show substantially faster acquisition by FSP than by other groups. Comparisons between FSP and YC monkeys show no overlap of individual scores for either total errors or sessions required to reach criterion performance on

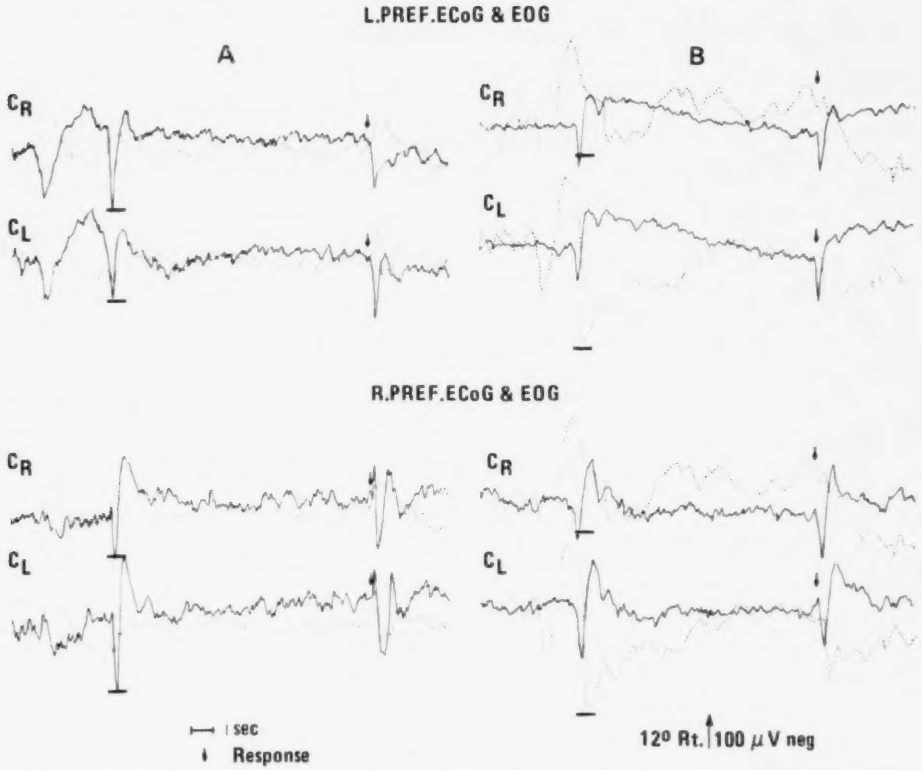

Fig. 1. Averaged left and right prefrontal electrocorticograms (solid lines) and concomitant electrooculograms (dotted lines, superimposed) during criterion performance of 12-sec delayed response for: (A) FSP 297 and (B) LEM 293. Separate averages (49 trials each) were obtained for trials when the cues were presented to the right (C_R) and left (C_L) positions. Horizontal lines denote 1-sec cue presentations. Arrows signify the beginning of the choice response period. Calibrations for ECoGs and EOGs are indicated. Upward deflections indicate cortical negativity or eye-deviations to the right.

Table 1. Acquisition of 12-sec Delayed Response Task by Groups of Monkeys with Differing Requirements for Trial Initiation[a]

Errors at each delay	Experimental group and monkeys												
	FSP[b]				YC[c]					MSP[d]		LEM[e]	
	295	297	314	298	302	301	315	292	294	313	316	293	114
2 sec	7	7	14	24	21	78	88	171	337	32	51	59	306
4 sec	4	16	2	20	8	41	136	84	42	4	86	41	7
8 sec	4	5	34	34	89	88	95	74	25	42	124	22	109
12 sec	4	8	10	20	3	24	31	21	76	7	65	2	30
Total errors	19	36	60	98	121	231	358	350	480	85	326	124	452
Total sessions	4	5	9	7	10	15	19	21	20	8	15	10	16

[a] Scores of errors and sessions include criterion performance of 88 correct responses in a 98-trial session.

[b] FSP - surface negative SP shift from left prefrontal cortex.

[c] YC - intertrial intervals yoked to those of monkeys in another group.

[d] MSP - surface negative SP shift from left precentral cortex.

[e] LEM - eye deviation to the right.

12-sec DR. Rapid acquisition by the FSP group is also indicated by the finding that one monkey responded at 90% correct during every training session and the others required few additional sessions. Although one MSP monkey (No. 313) acquired the task almost as fast as the FSP group, the other MSP was much slower. Since MSP and LEM groups consisted of only two monkeys each and their acquisition scores overlapped, they were combined for statistical analyses. Comparisons of total errors indicate significant differences between FSP and YC ($t=3.59$; $p<.01$), and between FSP and MSP-LEM groups ($t=2.19$; $p<.066$), but not between YC and MSP-LEM groups ($t=0.59$). Performance during off-line testing was evaluated by transfer scores between the last on-line and first off-line session at each delay setting. Mean transfer scores were above 92% for every group, indicating that monkeys indeed learned the DR task and could perform well without pre-cue requirements.

Results for 12-sec DR testing with brief cue presentations (Fig. 2) also showed better performance scores by FSP than by other groups. Only FSP monkeys continued to respond at the 90% criterion level during testing with brief cues. Performance differences between FSP and YC groups were significant for 0.1-sec cues ($t=4.91$; $p<.01$), but the differences were not significant for 0.2- or 0.5-sec cues. Low scores by the MSP group were the consequence of poor response by one monkey (316), which seemed unable to perform adequately under these conditions. Low scores by LEM monkeys for 0.2-sec and 0.1-sec cues may be attributed to an inability to detect cues in the left position.

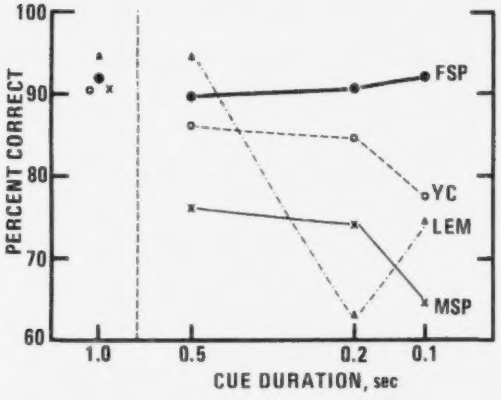

Fig. 2. Performance on 12-sec DR (two sessions, at 96 trials) with randomly presented cues of 0.5-sec, 0.2-sec, and 0.1-sec duration. The scores with 1-sec cues were obtained during the previous session. The testing contingencies for the different groups are indicated in Table 1.

Discussion

The results show impressive enhancement in learning the DR task when trial initiation is contingent upon computer-detection of prefrontal surface-negative SP shifts. Criterion performance to 12-sec DR by the FSP group was attained with about one-third the sessions and one-fifth the errors of the yoked control group. These scores indicate substantially greater facilitating effects on task acquisition than previously found with either low-voltage stimulation (Stamm 1964) or direct anodal polarization (Rosen and Stamm 1972) of prefrontal cortex. Enhancement was more pronounced when training was made contingent upon prefrontal than when it was contingent upon precentral negativity, although further study is needed to establish, clearly, the cortical specificity of effect. The functional significance of the prefrontal contingency is reflected, furthermore, by high transfer scores to noncontingent testing conditions. This finding indicates that the monkeys had indeed learned the task; i.e., their high performance was no longer dependent upon the contingent training procedure.

The present results support the view that the surface-negative SP shift is an important physiological phenomenon and an expression of neuronal activation (Fuster 1973, Niki 1974). The hypothesis that this electrocortical process reflects a heightened attentive state is supported by the results of DR performance with brief cues. Cues of 0.1-sec duration clearly require the monkey to be highly attentive in order to recognize the relevant cue. The finding that correct performance with a brief cue presentation was obtained only by FSP monkeys provides strong support for the attentive hypothesis.

Facilitated learning may only be possible when the crucial demands of the task occur during the trial epoch of maximum prefrontal negativity. This is the case for DR, which requires the monkey to recognize the location of the cue and program its choice response at that time. For other tasks that require optimal attention for selection of the choice response during other epochs of the trial, a requirement of pre-trial negative SP shifts may not lead to enhanced acquisition. This prediction was confirmed by an additional experiment (Gillespie 1977) in which the present monkeys were trained on a visually delayed matching-to-sample (DMS) task with the same pre-trial requirements as for DR. The FSP monkeys did not acquire the DMS task faster than their yoked controls.

The present investigation demonstrates that the acquisition of a difficult task can be facilitated by presenting cues contingent upon the occurrence of a specific cortical event. The prefrontal negative shift selected as the criterion event in monkeys is analogous to the CNV in humans (cf. Low et al. 1966). Walter (1966, 1967) demonstrated several years ago that external stimuli could be triggered by computerized detection of CNV-like negative shifts from humans. With the development of techniques for scalp detection of single electrophysiological events, it may be feasible to apply this method to the study of human learning and performance. With the detection of endogenous electrocortical events for trial initiation, it might be possible to enhance a subject's performance on attentive and cognitive tasks. The putative effects with this method may be of special benefit to subjects with certain cognitive and emotional disorders, such as mental retardation, learning disabilities, or schizophrenia.

Acknowledgments

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SUSTAINED ACTIVATION OF CORTICAL NEURONS IN STIMULUS-RECOGNITION TASKS[1]

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Studies of the effects of brain lesions on behavior have implicated certain cortical areas of the monkey in the integrative processes underlying performance of stimulus-recognition tasks. Delayed response (DR) and delayed matching-to-sample (DMS) are prime examples of such tasks. Their most distinctive feature is a period of delay interposed between a particular stimulus and a particular behavioral act predicated on the perception, retention, and recognition of information pertaining to that stimulus (Fig. 1). Inasmuch as correct performance of these tasks requires the temporary retention of sensory information, it is appropriate to consider them as tests of a certain form of memory variously designated as short-term memory, image memory, recent memory, or transient memory.

In the adult animal, the functional integrity of the prefrontal cortex is important for short-term memory. Animals with reversible dysfunction of the prefrontal cortex show a reversible deficit in performance of DR and DMS tasks that require temporary retention of spatial, kinesthetic, or visual information (Fuster and Alexander 1970, Fuster and Bauer 1974, Bauer and Fuster 1976). The deficit is closely dependent on the length of the delay. When that delay is zero or very brief, the deficit is not apparent; the deficit appears at longer delay and increases as a function of its duration (Fig. 2). Consequently, it seems that there is a neural process occurring during the delay for which the functional integrity of the prefrontal cortex is important.

In order to investigate that process, the activity of nerve cells in the prefrontal cortex and in related structures during performance of delay tasks has been explored. This exploration revealed a large proportion of neurons exhibiting increased firing during the delay (Fuster and Alexander 1971, Fuster 1973). The discharge of these neurons is higher on the average during this period than it is spontaneously, namely, between trials. Interestingly, many units show sustained activation during the delay but no activation during the preceding cue or the succeeding response of the animal (Fig. 3). Concomitant recording of EEG and EOG indicates that the phenomenon of sustained activation cannot be simply attributed to arousal or to eye movements. Both EEG arousal and eye movements are maximal during cue presentation and during the response period, not during the delay.

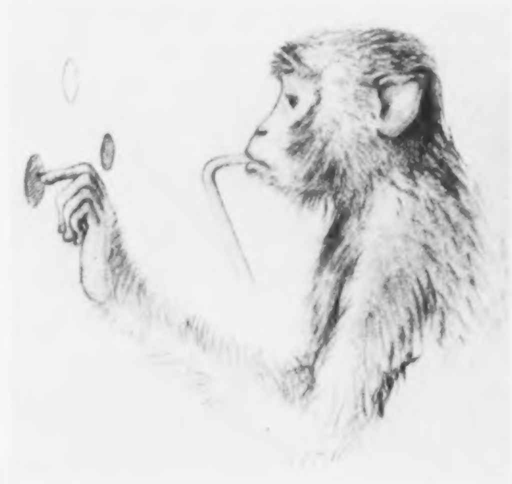

Fig. 1. Diagrammatic representation of a monkey performing stimulus-recognition tasks. Delayed response (DR): the stimulus (cue) is white light in one of the two lower stimulus-response buttons, the animal turns it off by pressing the button; a delay ensues, at the end of which both buttons are lit; the monkey is then rewarded with fruit juice for pressing the button that has been lit before the delay. Delayed matching-to-sample (DMS): the stimulus (sample) is a color, red or green, presented on the top button; after the delay, both colors appear in the lower buttons; reward is given for pressing the button with the sample color. Position of cue (in DR) and of colors (in DMS) is changed at random from trial to trial.

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[1] This research was supported by NIMH Research Scientist Award KO5 MH-25082 and NSF grant GB-41867.

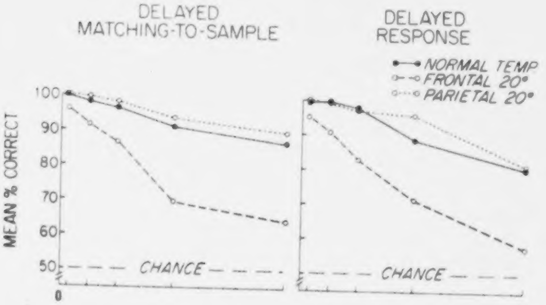

Fig. 2. Effects of cortical cooling on performance of DMS and DR. Note the delay-dependent deficit produced by cooling of lateral prefrontal cortex on the two tasks. No significant effect is produced by cooling parietal cortex.

There are some indications that prefrontal unit activation during the delay has something to do with the process of retention of information. A relationship has been seen between the level of activation of some units and the level of correct performance of the animal. Furthermore, certain control procedures indicate that the phenomenon is determined, at least in part, by the mnemonic attribute of the cue (Fuster 1973); however, the role of prefrontal units in retention is still obscure.

The temporal characteristics of cellular activation in the prefrontal cortex are particularly interesting and may bear on the generation of cortical slow potentials. Many units show the highest levels of discharge at the end of the cue period and beginning of the delay, when the information has just been presented and the waiting period begins. Sharp increases in firing are commonly observed at that time. Judging from individual unit records, there then appears to be a peak in probability of cell-firing within the prefrontal cortex. It is at that same time that Stamm and Rosen (1972), using a similar set of behavioral operations, have found a slow negative surface potential. This potential, which they relate to memory formation or registration, may be a manifestation of the underlying cellular phenomena mentioned above.

The search for the source and function of prefrontal unit activity in short-term memory led to the study of the visual transcortical pathway. This pathway has been anatomically well demonstrated. It is composed of a series of interlocking cortico-cortical connections that originate in the striate cortex and lead to the prefrontal cortex (Pandya and Kuypers 1969, Jones and Powell 1970). The last step of this pathway is constituted by connections between the inferotemporal and prefrontal cortices. Histological studies with silver impregnation techniques have established that these connections are bidirectional: the prefrontal cortex is not only the target of afferent fibers from the inferotemporal cortex but the source of efferent fibers running back to the inferotemporal cortex (Pandya et al. 1971).

This anatomical evidence provided part of the rationale for investigating the neuronal activity of the inferotemporal cortex during visual short-term memory tasks. This research was also encouraged by reports in the literature, mostly derived from ablation studies, indicating that the inferotemporal cortex is implicated in certain aspects of visual memory (Gross 1972, Mishkin 1972).

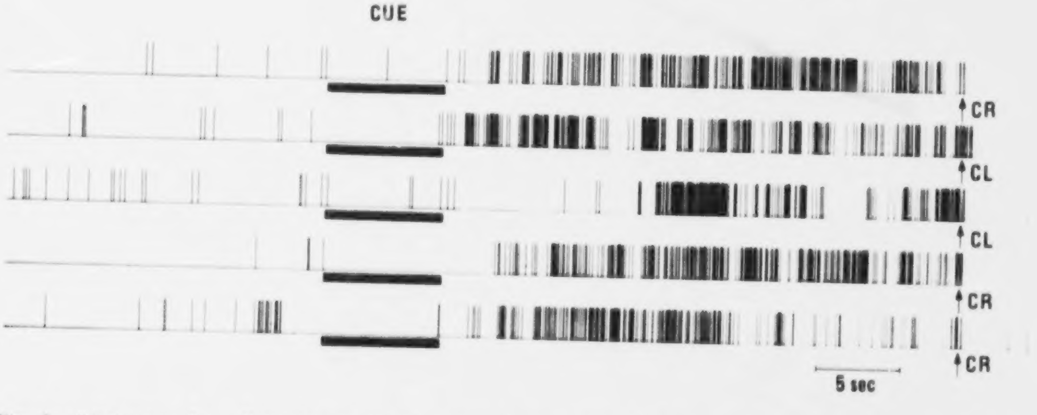

Fig. 3. Discharge of a cell in the prefrontal cortex during five trials of a direct-method DR task. At left, spontaneous discharge between trials. Horizontal bars mark the period of presentation of a positional cue—placement of food under one of two identical objects, one on the right and the other on the left. Between trials and during the intratrial delay, the objects are concealed behind a screen. Arrows mark the termination of delay, when the screen is raised and the two objects are presented for choice. Adjacent notations refer to the animal's response (C, correct; R, right; L, left). Note the increased discharge of the cell during the 32-sec delay.

A DMS task, using color as the sample or memorandum, has been recently utilized as the behavioral paradigm for examining the activity of inferotemporal neurons in visual short-term memory. So far, most of the records have been obtained by microelectrode penetrations of the anterior inferotemporal region, including areas of the middle temporal gyrus and posterior wall of the superior temporal sulcus. Many color-coded cells have been found in these areas. Such cells react differently to the sample depending on its color. When using a task with two colors (red and green), about the same proportion of units have been found to be activated preferentially by one color as by the other.

Again, as in the prefrontal cortex, sustained activation of discharge has been observed during the delay. Here, however, the level of activation is generally more related to the specific information which is relevant on each trial. This information in DMS depends exclusively on the wavelength of the sample color and is not spatially defined by position or configuration. This implies that whatever differences of firing are induced on a unit by the sample cannot be attributed or related to differences in motor activity, including eye movements.

In many inferotemporal units the level of firing during the delay is different depending on the color of the sample. In some of the units, differential firing is in fact only evident during the delay and not during the sample-presentation period (Fig. 4).

In our view, these observations are presumptive evidence that at least some units in the inferotemporal cortex are constituent elements of cortical neuronal assemblies that code and retain visual information. Because of the mentioned relationships between inferotemporal and prefrontal cortex, and because of the latter's role in delay tasks, we suspect that the retentive function of inferotemporal units is to some degree dependent on tonic influences from the prefrontal cortex. We have obtained some evidence, still sketchy and preliminary, that supports this hypothesis. Prefrontal cooling results in the diminution or disappearance of color-dependent differences in the discharge of some inferotemporal units during the delay. This occurs in conjunction with a drop in performance, which is indicative of poor retention.

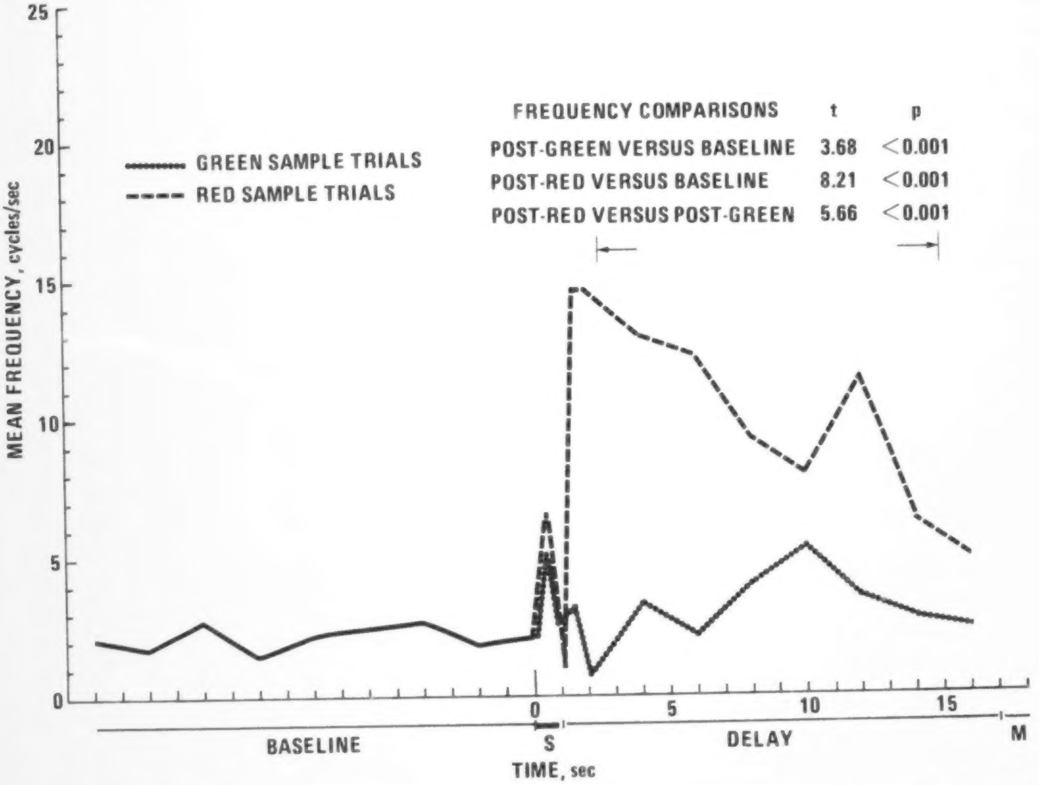

Fig. 4. Discharge of an inferotemporal cell during performance of DMS with two colors. S: sample; M: match. Firing is markedly increased during the delay of red-sample trials.

PRELIMINARY STUDY OF PHARMACOLOGY OF CONTINGENT NEGATIVE VARIATION IN MAN

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Although the contingent negative variation (CNV) was first described in 1964 (Walter et al. 1964), the electrogenesis of this phenomenon remains to be determined. The possibility that at least one putative neurotransmitter is involved in the generation of the CNV seems likely for at least two reasons. First, evidence is accumulating from neurophysiological, histological, and histochemical studies which suggests strongly that neurotransmitters are involved in neuronal transmission within the central nervous system, and there seems no good reason to exclude the genesis of the CNV from this possibility. Second, a large number of drugs have been shown to modify the CNV. These include ethanol (Kopell et al. 1972), carbon monoxide (Groll-Knapp et al. 1972), cannabis (Kopell et al. 1972, Low et al. 1973), flurazepam (Hablitz and Borda 1973), caffeine, nitrazepam, diazepam and cigarette smoking (Ashton et al. 1973, 1974, 1976), barbiturate and amphetamine (Kopell et al. 1974), and chlorpromazine (Tecce et al. 1975). On the other hand, little attempt has been made to use drugs as tools to analyse, systematically, the neuropharmacological mechanisms that subserve the CNV. In animals, Pirch (this volume) has shown that event-related slow potentials can be recorded (dc) from anterior cortex of the unanaesthetised rat and that drugs can be used to study the neuropharmacological mechanisms of the CNV under these conditions. The present study appears to be the first attempt of its kind in man.

The basic principle used in this pilot study was to examine the effect on the CNV of administering a drug with well-established selective blocking properties against a putative central neurotransmitter. It was predicted that, if any or all of the neurotransmitters played a role in the electrogenesis of the CNV, this fact would be reflected by an alteration in the record, most probably by a reduction in magnitude. Of several putative neurotransmitters likely to be involved, three were considered initially: (1) acetylcholine, (2) noradrenaline, and (3) dopamine, acting, respectively, on receptors designated as muscarinic cholinergic, α-adrenergic, and dopaminergic. Several pieces of evidence suggest that one or more of these neurotransmitters may be involved in the electrogenesis of the CNV. First, there is histological and histochemical evidence (Shute and Lewis 1967, Dahlstrom and Fuxe 1964, Ungerstedt 1971) on the distribution and interconnection of cholinergic, adrenergic, and dopaminergic systems in the brain. Second, the case for the role of acetylcholine has been cogently argued by Marczynski (this volume), while evidence for the role of dopamine comes from Libet (this volume).

The blocking drugs (pharmacological antagonists) used in this study are listed in Table 1. Each drug acts by competing with the corresponding neurotransmitter for the appropriate pharmacological receptors. A placebo, physiological saline, was also used.

Methods

Sixteen tests were conducted on 10 healthy, paid volunteers (6 male and 4 female), aged 18-30 years and of widely different occupations. Two of the male subjects and one of the female subjects took part in two, four, and three experiments, respectively; the remaining seven subjects took part in only one experiment. The project was approved by the local Hospital Ethical Committee.

A single-blind and pseudo-random design was used with one drug administered per experiment. EEG from the nasion + 2 cm, F3, F4, C3, Cz, C4, P3, P4 referred to linked mastoids was recorded with amplifiers modified to provide a 5-sec time constant. Eye movements were monitored by recording the vertical EOG. Movements of the right (button pressing) hand were recorded via the EMG. Electrocardiogram, respiration, and intermittent blood pressure were also recorded.

Table 1. Blocking Drugs (Pharmacological Antagonists) Used in This Study

Neuro-transmitter	Antagonist[a]	Dose
acetylcholine	atropine sulphate	0.4-0.5 mg
noradrenaline	thymoxamine HCl	0.08-0.l mg/kg
dopamine	metoclopramide HCl	5 - 7 mg

[a] Placebo was physiological saline solution 0.5 ml.

After control responses were obtained, a drug was injected into the right deltoid muscle, and the responses repeated. The intramuscular (I.M.) route was chosen as a compromise between oral and intravenous methods to avoid, respectively, the vagaries of gastrointestinal absorption and the risk of subjective effects of rapid attainment of blood levels.

CNV tests commenced at times (min): -28, -8, +2, +8, +16, +22, +36, and +56; and blood pressure (BP) at: -34, -22, -2, +14, +28, +42, and +62 relative to drug injection. For each set of recordings the subject received 24 trials. Sixteen trials uncontaminated by eye movements were selected for off-line computer averaging. Subjects lay on a bed with eyes open and fixated throughout.

Results

Atropine

Fig. 1 shows a series of eight CNVs recorded from one subject who received a dose of atropine after the second CNV. The figure clearly shows the subsequent decrease in CNV amplitude, which reached a minimum at 16-22 min with partial but irregular recovery in the CNVs that followed. The mean result obtained from four subjects is shown in Fig. 3a (t-test of CNVs at -8 and +22 min, $p < .02$).

Metoclopramide

Fig. 2 shows the result obtained in one subject. The mean result obtained in four subjects (Fig. 3b) shows a steady decrease in CNV amplitude, which reached a minimum at 36 min (t-test at -8 and +22 min, $p < .05$ and at -8 and +36 min, $p < .01$).

Thymoxamine and placebo

Neither thymoxamine (Fig. 3c) nor the placebo (Fig. 3d) produced a significant change in the mean CNV in four subjects.

Topographical effects

Corresponding changes in the CNV were observed in recordings made from adjacent electrode sites. Preliminary analysis indicated no topographical localization of drug effects.

Reaction time

RT to the imperative stimulus (S2) showed no change with atropine or placebo, but it was lengthened by as much as 30% with metoclopramide and shortened by 15% under the influence of thymoxamine, in spite of the fact that the latter drug had no detectable effect on the magnitude of the CNV. These changes in RT were statistically significant (t-test, $p < .001$).

Blood pressure and respiration were not affected by any of the drugs used in this study.

Subjective effects

With one exception, none of the subjects complained of any subjective effects during the experiments. About 10 min after the injection of atropine, one subject complained of transient blurring of vision, making it difficult to see the fixation spot.

Discussion

Preliminary results indicate that the CNV is depressed by atropine and metoclopramide, but is unaffected by thymoxamine and placebo administration. It was important that the doses of drugs used did not produce significant subjective effects which might have confounded interpretation of the direct drug-induced effects on the CNV. Since thymoxamine has a very short plasma half-life (c. 10 min), it is possible that no effect would be seen with intramuscular drug administration. It is important, therefore, to study the effects of thymoxamine administered by intravenous infusion to maintain more constant blood and brain levels during CNV recording.

These results suggest that both cholinergic muscarinic and dopaminergic mechanisms are involved in the generation of the CNV, although the data do not provide any direct indication of the neuroanatomical site(s) involved. The results support hypotheses that both a cholinergic mechanism (Marczynski, this volume) and a dopaminergic mechanism (Libet, this volume) are involved in the genesis of the CNV.

The present findings are not incompatible with Somjen's proposal (this volume) that the CNV may

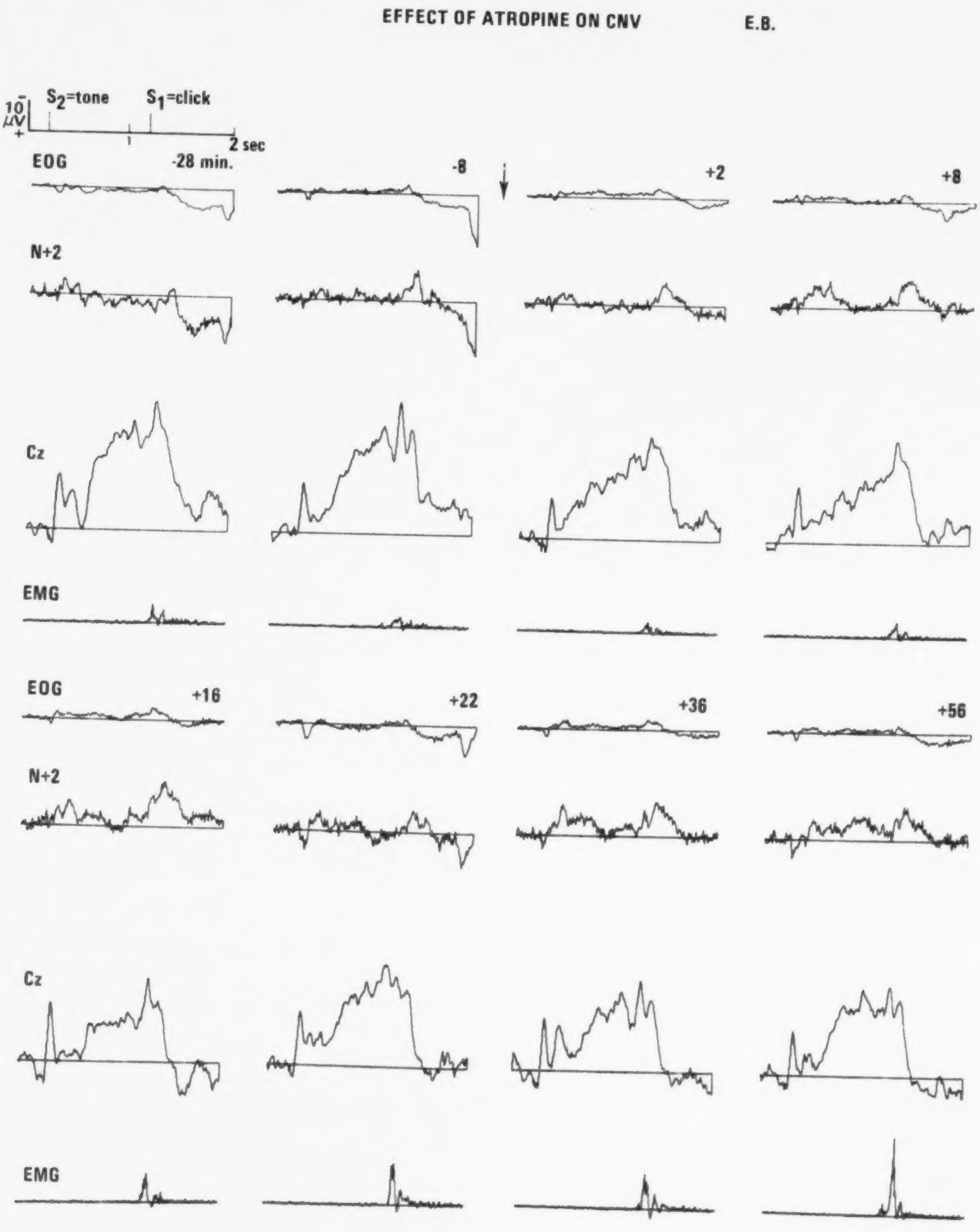

Fig. 1. Effect of atropine 0.4 mg I.M. injection (at arrow) in one subject. N+2 refers to an electrode 2 cm above the nasion.

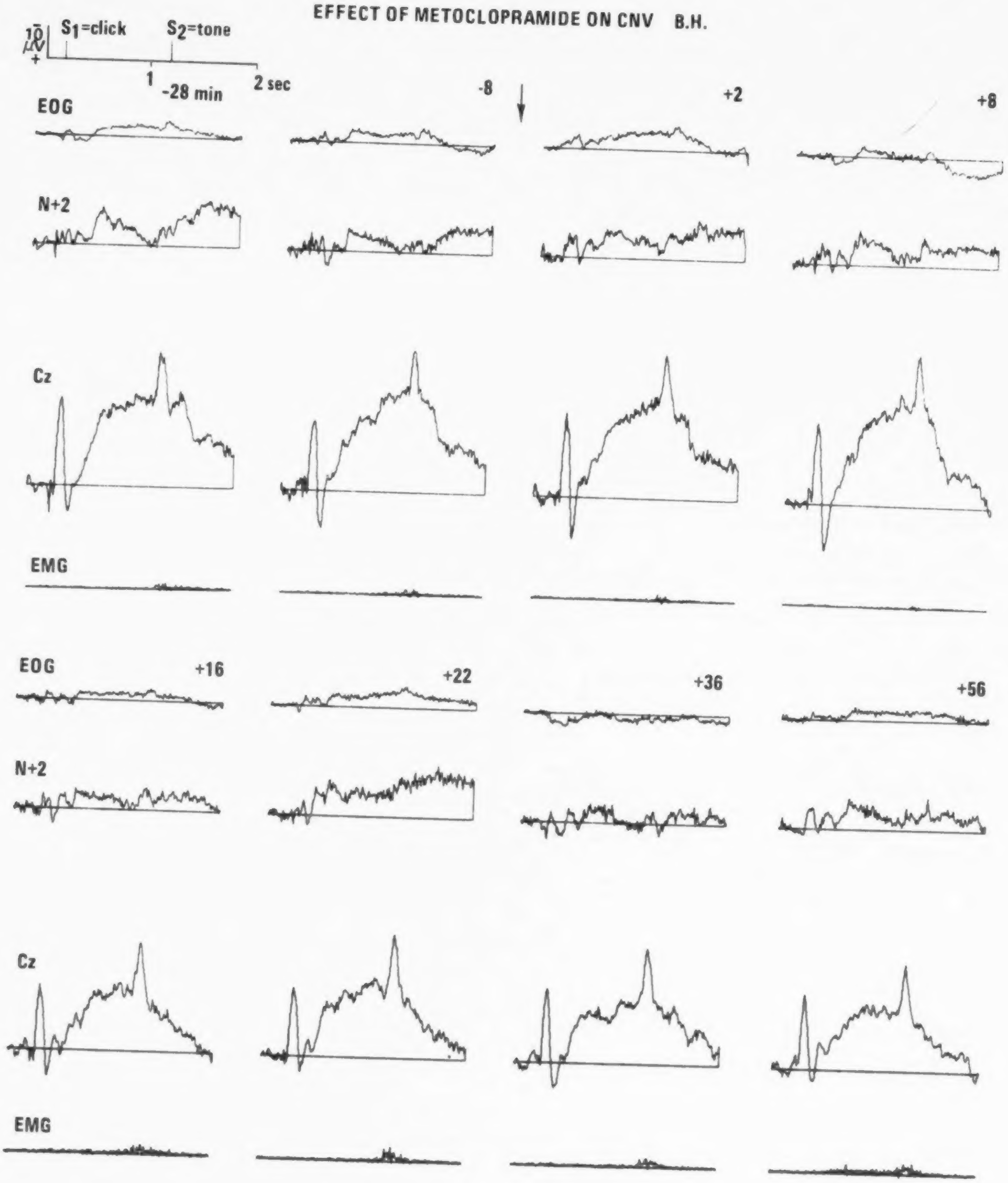

Fig. 2. Effect of metoclopramide 7 mg I.M. injection (at arrow) in one subject.

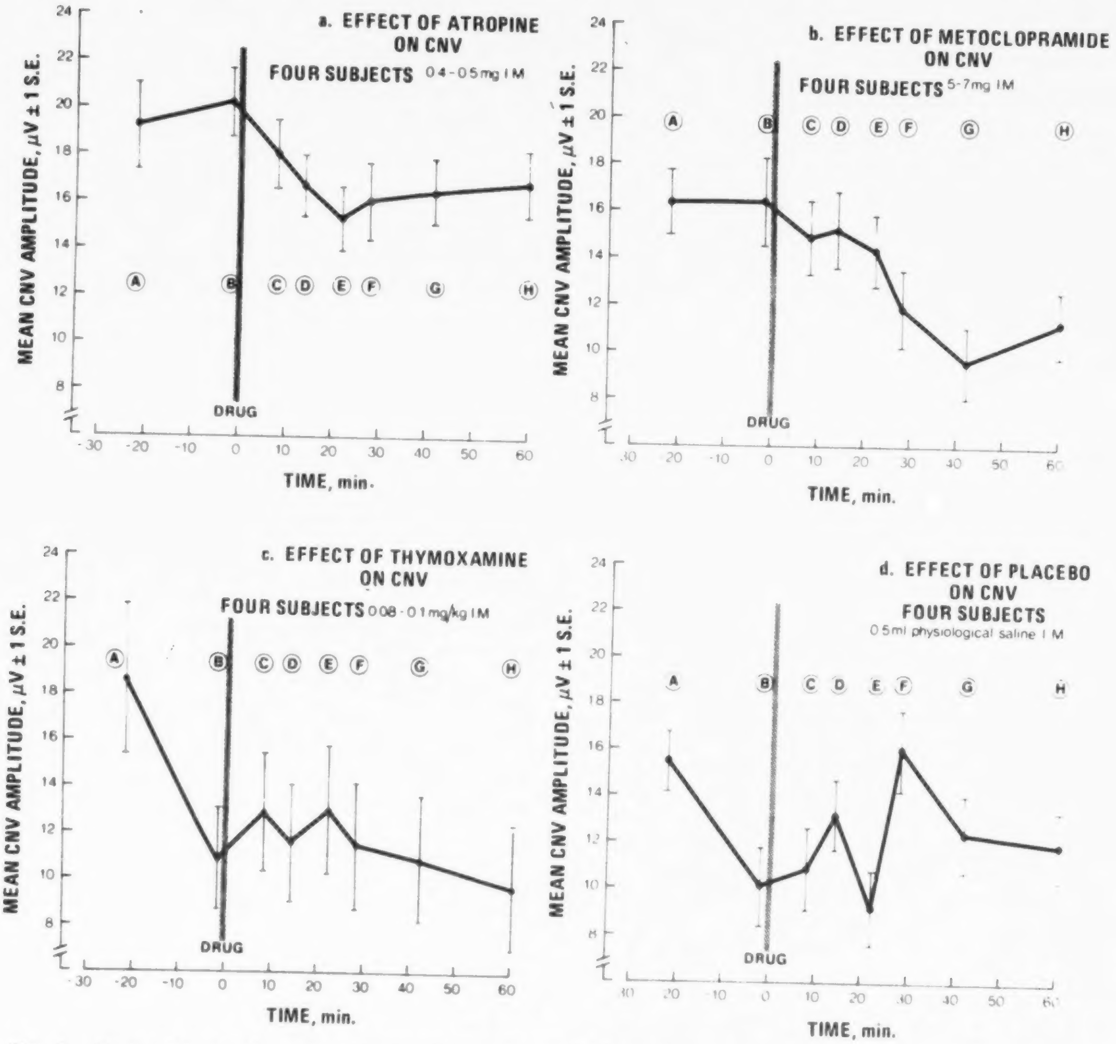

Fig. 3. Mean effect in four subjects of (a) atropine (0.4-0.5 mg I.M.), (b) metoclopramide (5-7 mg I.M.), (c) thymoxamine (0.1 mg/kg I.M.) and (d) placebo (physiological saline 1 ml I.M.) on CNV. Drug injected at t_0.

be generated by depolarization of glial cells. Somjen conjectures that glial cell depolarization is determined by the extracellular potassium concentration which, in turn, depends upon the activity of adjacent nerve fibres. If atropine or metoclopramide block transmission in a substantial number of nerve fibres, the reduced neuronal activity would be accompanied by a decrease in extracellular potassium concentration and, consequently, a reduced CNV.

Whether or not glial cells are involved in the electrogenesis of the CNV, it is reasonable to postulate that the generation of the CNV depends upon the integrity of cholinergic muscarinic pathways in the ascending reticular activating system. Dopamine may enhance cholinergic transmission in these pathways by inducing a synaptic change in cholinergic receptors similar to those concerned with slow muscarinic or s-EPSP responses in ganglia (Libet and Tosaka 1969). Further experiments in man are planned in which a range of drug doses will be used to extend the present pharmacological analysis.

Acknowledgment

The authors wish to thank Dr. B. M. Guyer, William R. Warner & Co. Ltd., for the donation of thymoxamine HCl and Miss D. Mustart and the Department of Photography and Teaching Aids Laboratory, University of Newcastle upon Tyne, for preparing the figures.

EFFECTS OF AMPHETAMINE AND PENTOBARBITAL ON EVENT-RELATED SLOW POTENTIALS IN RATS[1]

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Investigations concerning the effects of drugs on event-related slow potentials (ERSP) in unanesthetized, behaving animals are relatively few (Caspers 1963; Marczynski et al. 1969; Marczynski 1971, 1972b; Norton and Jewett 1967; Pirch and Norton 1967a, 1967b; Pirch and Osterholm 1975), and studies of the effects of drugs on the human contingent negative variation (CNV) have yielded varying results (Kopell et al. 1972, Low et al. 1973, Braden et al. 1974, Tecce and Cole 1974, Kopell et al. 1974). Thus, the effects of different classes of drugs on ERSPs are incompletely characterized, and, as a result, interpretation of the meaning of drug effects is uncertain. For example, it appears to be widely accepted that ERSP amplitude is increased by "stimulant" drugs and decreased by "depressant" drugs. Tecce and Cole (1974) reported, however, that amphetamine may either increase or decrease CNV amplitude and Ashton et al. (this volume) found that nicotine has a biphasic action on CNV amplitude. Additional knowledge of the effects of drugs on slow potentials would be of value not only for interpretation of drug-induced alterations of ERSP but also as a data base for evaluating changes induced by toxic environmental substances. Accordingly, this paper is a brief report of some of the studies conducted in our laboratory to characterize drug effects on slow potentials recorded from the cortex of rats trained on various behavioral paradigms.

Methods

Female albino rats were housed individually during the experimental period. Twenty-two gauge silver wires were coated with silver-chloride and were implanted under pentobarbital and ether anesthesia after atropine pretreatment. The electrodes were in contact with the active or reference site via agar-saline pools (1% agar-1% saline). Artifact due to pulsation of the brain was reduced by making the bridge with two pieces of polyethylene tubing filled with the agar-saline. One piece (PE 90) was fitted onto the electrode and was inserted into the other (PE 240) which rested on the recording site. The dura was left intact over the active recording site. The bone reference electrode was inserted into an agar-saline pool formed by the polyethylene tubing placed in a small depression drilled in the bone. The active electode was placed over the cortex 2-3 mm anterior to the bregma and to the right of midline. A reference was placed approximately 2 mm anterior to the parietal-interparietal suture on the left side either in bone (in the discrimination experiment) or on the dura (in the operant experiment). In other experiments with the operant paradigm used here, there was little difference between SP responses when the reference at this site was in bone, on dura or on lesioned cortex. On the other hand, if the cortex under the active electrode was damaged, SP response amplitude was markedly decreased. EEG was recorded using preamplifers set for dc recording. The 3-Hz half-amplitude high frequency filter on the driver amplifier of one channel was used to obtain a recording of the dc potential change without the associated EEG.

Discrimination procedure

For conditioning and recording, animals (n=8) were placed individually in a clear Plexiglas chamber 10 x 10 x 7.5-in. high with a grid floor. Before electrode implantation, the animals were trained to associate the delivery of reinforcement (45-mg food pellet) with the sound of the delivery device so that they would approach the feeding dish on hearing this cue, thereby allowing associative conditioning to other auditory cues. Two tone bursts of 0.5-sec duration were employed for discrimination conditioning;

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one (S^d) was followed after 3 sec by the delivery of a food pellet while the other (S^Δ) was not reinforced. The two stimuli were 400-Hz and 4500-Hz tones at 50dB. For some animals the 400-Hz tone served as S^d, whereas the 4500-Hz tone was reinforced in others. S^d and S^Δ were given on alternate trials. Intertrial intervals varied between 45 and 90 sec. Thirty trials were given in a single session (15 trials with each stimulus), and only one session was conducted per day. The animals had free access to Purina Laboratory Chow during one hour at the end of each day.

Voltage changes during the 3-sec period following the onset of the conditioned stimulus were measured at each 0.25-sec interval using a Tektronix 31/53 data acquisition system. The area of the averaged SP response to each stimulus was calculated and these values were used for statistical comparisons and illustrations.

d-Amphetamine sulfate was dissolved in 0.9% saline and was administered intraperitoneally 30 min before trials began. Saline was given before each control session during the drug testing phase.

Operant procedure

Before electrode implantation, eight animals were trained to obtain food reinforcement by pressing a lever when it extended into the chamber. The lever was made of nonconducting acrylic. In the final behavioral schedule, the retractable lever began to move into the chamber 2 sec following the onset of a 20-msec auditory warning stimulus (1600 Hz, 90dB). Once the lever was activated (approximately 3.9 sec after the onset of the trial), the rat had 2 sec to obtain reinforcement. The lever was inactivated and retracted either when pressed or 2 sec after becoming activated. Intertrial intervals varied between 18 and 70 sec. Sixty to 65 trials were given in a single session and only one session was conducted per day. Acquisition of slow potential data began after the first 20 acclimation trials.

EEG was recorded as described above. Output from the polygraph was fed into a Nicolet MED-80 Data Acquisition and Analysis System. An additional channel was used to record the lever-press, and the signal was also fed to the computer for analysis of response latencies. The data for each trial (including 500 msec of prestimulus baseline data) were digitized at a rate of 78 samples per second and stored on a floppy disk. At the end of the session, artifact-free trials were averaged, lever-press latencies were measured, and the maximum negative amplitude of the averaged waveform was determined. The mean of 39 samples obtained during the 500 msec prestimulus period served as zero baseline.

d-Amphetamine sulfate was administered intraperitoneally 30 min before data acquisition began and pentotarbital sodium (dissolved in distilled water) was given subcutaneously 15 min before acquiring data. Results are reported for those animals in which SP responses remained sufficiently artifact-free for a long enough period of time to allow administration of all doses of a drug to an individual rat.

Baseline correlations

In most animals, the recording electrodes were sufficiently stable that little or no drift occurred during the experimental session. During the initial 20 acclimation trials the potential difference between the two electrodes was balanced and no further adjustment was made. Through the use of the data acquired with the 3-Hz half-amplitude high frequency filter, the prestimulus dc baseline values obtained for each trial during the operant schedule were stored, the most positive baseline for any trial in the session was found, and this value was subtracted from all baseline values (i.e., the most positive baseline was adjusted to zero and all other baselines were negative relative to this point). The maximum negative amplitude was also determined for each trial. The Pearson product-moment correlation coefficient was calculated to examine the relationship between baseline and amplitude. All measurements and calculations were performed by the computer.

Results

When the conditioned stimulus was presented without reinforcement, initially observed negative slow potential (SP) responses decreased in amplitude after a few sessions. This habituation developed to each conditioned stimulus used in these experiments. When reinforcement was instituted, the amplitude of the SP responses increased several fold and reached maximum within a few sessions. Polygraph tracings of SP responses during four trials in one rat trained in the operant procedure are shown in the left panel of Fig. 1. The right panel of Fig. 1 illustrates the averaged SP response of 40 trials in the session. The negative slow potential response began shortly after the stimulus and retruned to baseline following the delivery of reinforcement. In some cases a positive shift developed after reinforcement, similar to the postreinforcement positive shift observed in cats by Marczynski et al. (1969).

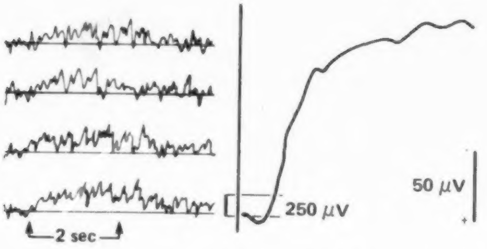

Fig. 1. EEG recordings and averaged SP response from a rat performing the operant task. Left panel: recordings from four single trials; first arrow indicates onset of warning stimulus; time between arrows is 2 sec; calibration is 250 μV; negative is up. Right panel: average of 40 trials in session from which the single trial recordings were obtained; sweep time is 2 sec; calibration is 50 μV; negative is up.

Discrimination procedure

The first 10 training sessions on the discrimination schedule demonstrated a phase of stimulus generalization during which large SP responses developed to both stimuli. By session 12, the responses to the reinforced stimulus (S^d) were significantly greater than responses to the nonreinforced stimulus (S^Δ) (t-test for paired comparison of SP response areas, $p < .05$). This difference increased and persisted throughout the remaining 25 or more sessions.

Amphetamine produced a dose-related depression of SP responses to the reinforced stimulus at doses of 0.25 to 2 mg/kg (Fig. 2a). The effect on responses to the nonreinforced stimulus was, however, biphasic and depended upon the dose. The lower doses (0.25 and 0.5 mg/kg) enhanced the responses, the intermediate dose (1mg/kg) produced no change, while the high dose (2 mg/kg) depressed the SP responses (Fig. 2b). Examination of the effects of 0.5 mg/kg clearly shows that this dose of amphetamine depressed the responses to S^d at the same time that responses to S^Δ were enhanced. These experiments illustrate the importance of dose and of stimulus significance in determining the action of drugs on event-related slow potential responses.

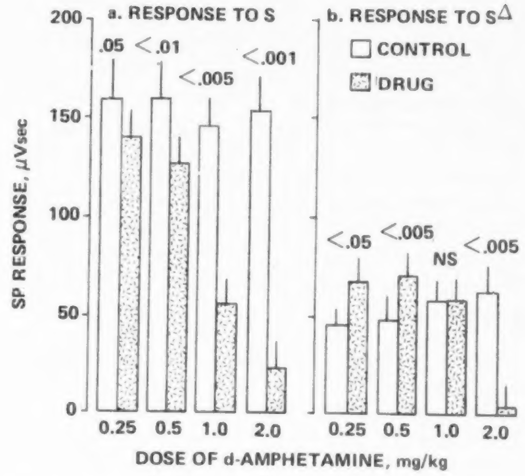

Fig. 2. Effect of d-amphetamine on SP responses to reinforced (S^d) and nonreinforced (S^Δ) stimuli. Each bar represents the mean of SP responses (calculated areas) from eight animals. Vertical lines are standard errors. Open bars show the responses after saline treatment while shaded bars show the responses after treatment with various doses of d-amphetamine. Responses were negative in polarity. P values are based on paired-t comparisons.

Operant procedure

Fig. 1 shows samples of single trial SP responses in one animal, recorded during performance of the operant task, and Fig. 3 illustrates averaged SP responses in four different animals, obtained in control sessions. Mean lever-press latencies for control sessions ranged from 70 to 750 msec after lever activation, depending upon the animal.

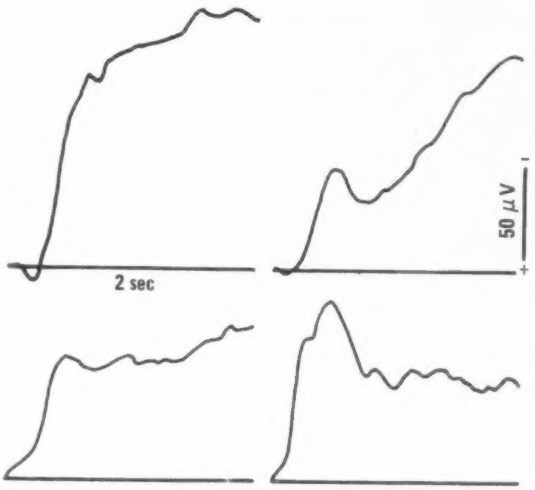

Fig. 3. Averaged SP responses from control sessions in four different animals performing the operant task. Average of 40 trials. The time of each response is the 2-sec period following the onset of the warning stimulus. Negative is up.

Both d-amphetamine and pentobarbital caused a dose-related reduction of the amplitude of SP responses (Fig. 4). The doses of amphetamine were 0.25, 0.5, and 1.0 mg/kg while pentobarbital was given in doses of 5, 10, and 15 mg/kg. The number of lever-presses was unaffected by the two lower doses of amphetamine and there were no consistent changes in latency. After 1 mg/kg, the four animals shown in Fig. 4 obtained reinforcement in 98, 93, 63, and

50% of the trials and the lever-press latencies were not significantly altered. The three animals treated with pentobarbital obtained 100% reinforcement after 5 mg/kg; 98, 88, and 50% after 10 mg/kg; and 38, 10, and 0% after 15 mg/kg. There were no consistent changes in lever-press latencies, with some animals showing increases and others decreases as compared with the previous control session. It appears that if lever presses occur after drug treatment, they are within the range of control latencies. The averaged SP responses for trials in which the animals obtained reinforcement were larger than the responses for trials in which no lever press was made.

These experiments indicate that both stimulant and depressant drugs can suppress event-related slow potentials recorded from the rat cortex during an operant task. Under the conditions of these experiments, the slow potential response was a more sensitive indicator of drug effect than the behavioral measure.

Baseline correlations

Slow potential responses to the warning stimulus were greater in amplitude during those trials in which the baseline dc level was more positive as compared with the amplitude of responses in trials with more negative baselines. Fig. 5 illustrates this relationship for a session in one animal. Averaged SP responses for the 20 trials with the more positive (larger response) and the 20 trials with the more negative baselines are shown in the insert. Significant inverse correlations between baseline negativity and SP response amplitude were observed in eight rats in which baseline correlations were studied. These experiments indicate that the magnitude of slow potential change in response to a conditioned stimulus may vary according to the dc potential level at the time of stimulus presentation.

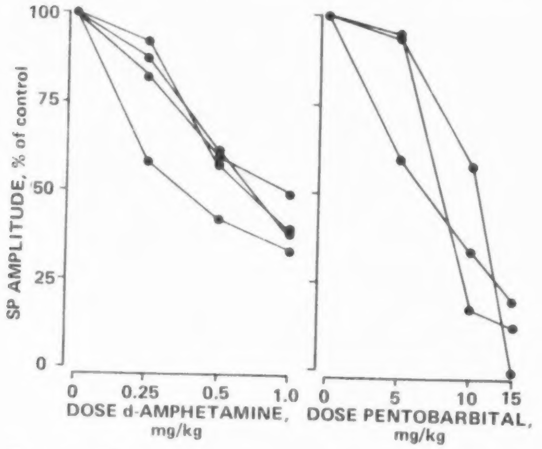

Fig. 4. Effects of d-amphetamine and pentobarbital on SP responses associated with the operant task. SP response amplitude is plotted as percent of the amplitude of the vehicle control sessions with each rat serving as its own control. Each curve represents an individual animal.

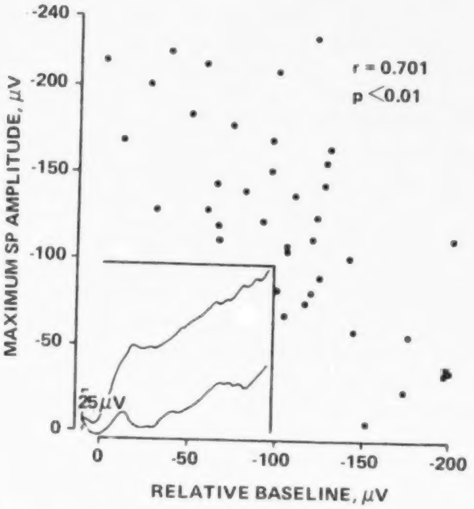

Fig. 5. Relationship between baseline dc potential and SP response amplitude. Data from 40 trials of a single operant session in one rat. See text for complete description. Averaged SP responses for the 20 trials with the more positive (larger response) and the 20 trials with the more negative baselines are shown in the insert. Calibration is 25 µV. Negative is up.

Discussion

The results of these studies indicate that event-related slow potential responses recorded from the cerebral cortex of rats are altered by stimulant and depressant drugs in a dose-dependent manner. Furthermore, the experiments utilizing a discrimination procedure suggest that the drug effects are also dependent upon the behavioral significance of the eliciting stimulus. Thus, with a single drug one may observe enhancement or depression of SP responses. With appropriate doses and behavior schedules, drugs which are members of different pharmacological classes can produce similar effects on SP response. The fact that drugs with different modes of action can cause similar alteration of event-related slow potentials suggests that caution should be exercised in interpreting the meaning of a drug effect, especially when based on single-dose or even two-dose studies.

It is clear that chemical agents which affect arousal mechanisms produce changes in ERSP amplitudes. Other factors which alter arousal such as the experimental setting or behavioral task can also be expected to influence slow potential responses. A role for arousal mechanisms in determining amplitude of the CNV was proposed by Irwin et al. (1966) and Rebert et al. (1967). Tecce (1972) further suggested that an inverted-U relationship exists between level of arousal and amplitude of slow potentials. Using Tecce's model, one might predict that if the arousal level were optimal for maximum SP amplitude under the conditions of the experiment, either an increase in arousal induced by a stimulant drug or a decrease in arousal produced by a depressant drug could cause a reduction of the slow potential amplitude. Such a model might apply to the effects of amphetamine and pentobarbital in the present experiments using the operant task. In other studies with rats trained on a simpler paradigm in which food reinforcement was automatically delivered, both d-amphetamine and pentobarbital reduced SP response amplitude (Pirch and Osterholm 1975). When doses of each agent which depressed SP amplitude were combined, the SP response was restored to control levels. Those results would be consistent with the concept of an inverted-U relationship between arousal and SP amplitude. Arousal is difficult to define, however, and some other process such as attention may be more directly related to amplitude of slow potentials. Although some consistent relationships appear to exist between arousal and ERSP amplitude, the effects of amphetamine on the discrimination procedure suggest that other processes may also play a role.

An additional factor which has been proposed to affect ERSP amplitude is the baseline dc potential. Knott and Irwin (1968) suggested a "ceiling effect" whereby greater negativity of the dc level at the time of stimulus presentation results in a limitation of the negative slow potential change which can develop in response to the stimulus. The results of the dc baseline studies reported here are consistent with the "ceiling" hypothesis. Additional experiments are under way to determine whether the drug-induced changes in SP responses are related to alterations of the baseline dc level.

CHOLINERGIC MECHANISM OF SLEEP ONSET POSITIVE VARIATION AND SLOW POTENTIALS ASSOCIATED WITH K-COMPLEXES IN CATS

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In the cat, sleep onset is characterized by high-voltage, rhythmic (7 to 9 c/sec), alpha-like bursts over the parieto-occipital cortex with highest amplitude over primary and secondary visual projections. These electrocorticogram (ECoG) patterns are always associated with large epicortical positive slow potentials (SPs) the amplitude of which ranges from 200 to 500μV if recorded epidurally with reference to subjacent white matter or a distant relatively indifferent electrode located over the anterior ectosylvian gyrus. Since this localized SP always occurs during sleep onset, it was termed "sleep onset positive variation" (SOPV) (Marczynski et al. 1971b).

During slow wave sleep (SWS) mild auditory, somatosensory, or visual stimuli trigger K-complexes that are immediately followed by bursts of alpha-like activity and SPs whose topograpical distributions are virtually identical with those of SOPV (Marczynski et al. 1969). The assumption that the SOPV phenomenon reflects an active process of internal inhibition in the Pavlovian sense is supported by the observation that, in a relaxed cat, 7- to 9-c/sec flash stimuli produce responses indistinguishable from SOPV and shorten the period necessary for the emergence of SWS (Marczynski and Sherry 1972). Hence, the SP associated with K-complex (K-SP) can be regarded as reflecting a homeostatic mechanism aimed at maintaining SWS.

In the present study, the effect of mild auditory, somatosensory, visual, and vestibular stimuli were investigated in the cat on the emergence of K-SP prior to and after administration of scopolamine hydrobromide. In addition, the SOPV phenomenon was also quantified prior to and after drug administration.

Methods

Four adult cats were used. Under pentobarbital anesthesia, Ag/AgCl electrodes were implanted epidurally over the posterior marginal (M), medial suprasylvian (S) and anterior ectosylvian gyri (E). The technique of implantation, recording, and integration of SPs, using Grass cumulative integrators, has been previously described (Marczynski et al. 1971b). The output of the integrator was adjusted to produce two pen deflections in response to a positive shift of 100μV lasting 1 sec. This value was accepted as one unit of SP. Only the SP between the S and M gyri were quantified and used for statistical evaluation, using the Student's t-test. Experiments were conducted in a 1-m^3 sound-attenuating Lehigh Valley test chamber provided with dim light and a one-way window. Auditory stimuli of approximately 6 dB above background noise were presented through a loudspeaker attached to the ceiling. The Grass visual stimulator unit, modified to produce noiseless flashes, was also attached to the ceiling. Electric somatic stimulation was delivered through a pair of stainless steel electrodes implanted subcutaneously on the cat's back. The electrodes were connected to a Grass S-8 stimulator and stimulus isolation unit; the parameters of stimulation employed were 3 - 5V and 0.5 - 0.8 msec duration. Experiments were conducted between 2 and 5 p.m. One hour prior to the session, the cat was provided with food and milk. After satiation, the cat was allowed to sleep in the basket suspended by strings from the ceiling of the chamber such that, when one string was pulled, the basket would sway to provide vestibular stimulation. K-SPs were quantified by counting the number of integrator deflections during a 7-sec time period following stimulus presentation. At least 10 K-SPs were obtained for each modality and each dose of scopolamine hydrobromide. SOPV responses were quantified by counting integrator deflections from the moment the cat assumed sleep posture to the emergence of SWS lasting at least 10 sec. Output of the integrator was set to zero when the cat assumed sleep posture. If for any reason the cat did not develop SWS, raised the head, or left the basket, the record was disregarded.

Results

SOPV responses

In most instances, 4 to 7 SOPVs, each lasting 3 to 12 sec, were observed prior to the emergence of SWS. Fig. 1A shows three SOPV responses in one cat. Usually, after the first and second SOPV, a "residual" positivity was observed, larger over the M gyrus and smaller over the S gyrus, thus causing a tonic SP shift below baseline in the S-M lead and above baseline in the S-E lead. Residual SPs did not continue to accumulate with subsequent SOPVs and tended to dissipate with the onset of SWS (marked with a vertical dashed line) as shown in Fig. 1A (right) and 1B (left) of the continuous record. The use of the S gyrus as the reference caused the typical mirror reversal patterns due to the decreasing potential gradient along the M-SOE line. A detailed description of the topographical distribution of the SOPV has been reported elsewhere (Marczynski et al. 1971b).

During control sessions, the sum across cats of SOPV responses observed from the moment the animal assumed sleep posture to emergence of SWS ranged from 46 to 105 Units (mean 56.7; S.D. ± 3.4; N = 50). In cats treated with scopolamine hydrobromide (0.02 mg/kg, i. m.) 30 min prior to a session, this value was reduced by 27.6% (S.D. ± 0.6; $p < 0.01$). The dose of 0.04 mg/kg reduced responses by an average of 55.3% (S.D. ± 0.08; $p < 0.0001$). After the latter dose, the alpha-like bursts during SOPV responses never occurred in long rhythmic trains, but were often interrupted by irregular delta waves. Despite the conspicuous reduction in the amplitude of SOPVs, their duration (6.7 sec per single response; S.D. ± 1.4) was not significantly different than that of the control SOPV (7.1 sec; S.D. ± 1.9;$p < 0.05$). After higher doses of scopolamine (0.06 mg/kg, i.m.), the background amplitude of the ECoG increased and it was difficult to decide when the SWS emerged. Choppy alpha-like bursts, if present, were associated with small SP shifts (Fig. 1 bottom left).

K-complex SP (K-SP)

The control K-SP in response to an auditory (A), somesthetic (S), vetibular (V) or flash (F) stimulus are shown in Fig. 1B. The patterns and topographical distributions of these responses were virtually identical for all modalities tested and closely resembled those of the SOPV. In cats treated with scopolamine (0.02 mg/kg i.m.), K-SPs were reduced by an average of 32.2% (S.D. ± 0.7; $p < 0.01$), and doses of 0.04 mg/kg reduced these responses by 67.4% (S.D± 0.9; $p < 0.001$). As shown in Fig. 1C (right), a dose of scopolamine 0.06 mg/kg almost totally suppressed these responses and the EcoG and SP remained "frozen" within a relatively narrow band of fluctuations.

Discussion

Since scopolamine blocks SOPV and K-SP responses, it most likely interferes with the process of internal inhibition. With moderate doses of scopolamine, the duration of "abortive" SOPVs did not change, although their amplitude was reduced. This indicates that "primary" hypnogenic influences which trigger SOPV responses are not affected, but the "execution" of SOPVs is impaired, most likely at the thalamocortical level. Likewise, scopolamine suppresses alpha-like postreinforcement ECoG synchronization (PRS) and the associated reward contingent positive variation (RCPV) in cats trained to lever press for milk reward, although the duration of the choppy PRS and that of the abortive RCPV responses is not significantly changed (Marczynski 1971).

The phasing theory of neuronal activity, based on recurrent inhibitory circuits in the thalamus, which are reputed to control alpha rhythm, implies that a certain level of "synaptic pressure" is necessary to initiate and drive the phasing circuits (Andersen and Andersson 1968). Numerous microelectrophoretic studies of single neurons in specific thalamic relay nuclei (Steiner 1968, McCance et al. 1968, Tebecis 1970, Phillis 1971) suggest that the primary role of cholinergic projections described by Shute and Lewis (1967) is facilitation of sensory input. Hence, blockade of cholinergic influences may result in reduction of synaptic pressure to a level insufficient to initiate and drive phasing circuits in thalamus and cortex. Evidence that further supports this contention and the hypothetical interactions between cholinergic and monoaminergic projections that seem to control the phasing mechanisms have been discussed elsewhere (Marczynski and Burns 1976 and this volume).

The occurrence of SOPV and K-SP in association with alpha-like bursts can be interpreted as resulting from a phasic tendency toward hyperpolarization of large populations of neurons in the cortex and electrotonic spread of IPSPs to apical dendrites which is reflected as surface positivity (Creutzfeldt et al. 1969). During bursts of alpha activity in the thalamus (Andersen and Andersson 1968) and visual cortex (Creutzfeldt et al. 1969), many neurons show primary IPSPs (i.e., not preceded by EPSPs) and may remain silent in a state of hyperpolarization. These neurons are the most likely source of phasic surface positive SPs associated with alpha-like bursts. The participation of glia cells may be secondary to phasic changes in concentration of ions in the extraneuronal fluid.

The virtually identical patterns and distribution of SOPVs and K-SPs triggered by various modalities can be explained by the fact that, in the visual cortex, there are neurons that respond to auditory, somesthetic, and vestibular stimuli (cf. Morrell 1972). The equipotential role of various modalities in generating K-SPs and their localization over primary and secondary visual projections indicate that striate and parastriate cortex plays a dominant role in internal inhibitory processes.

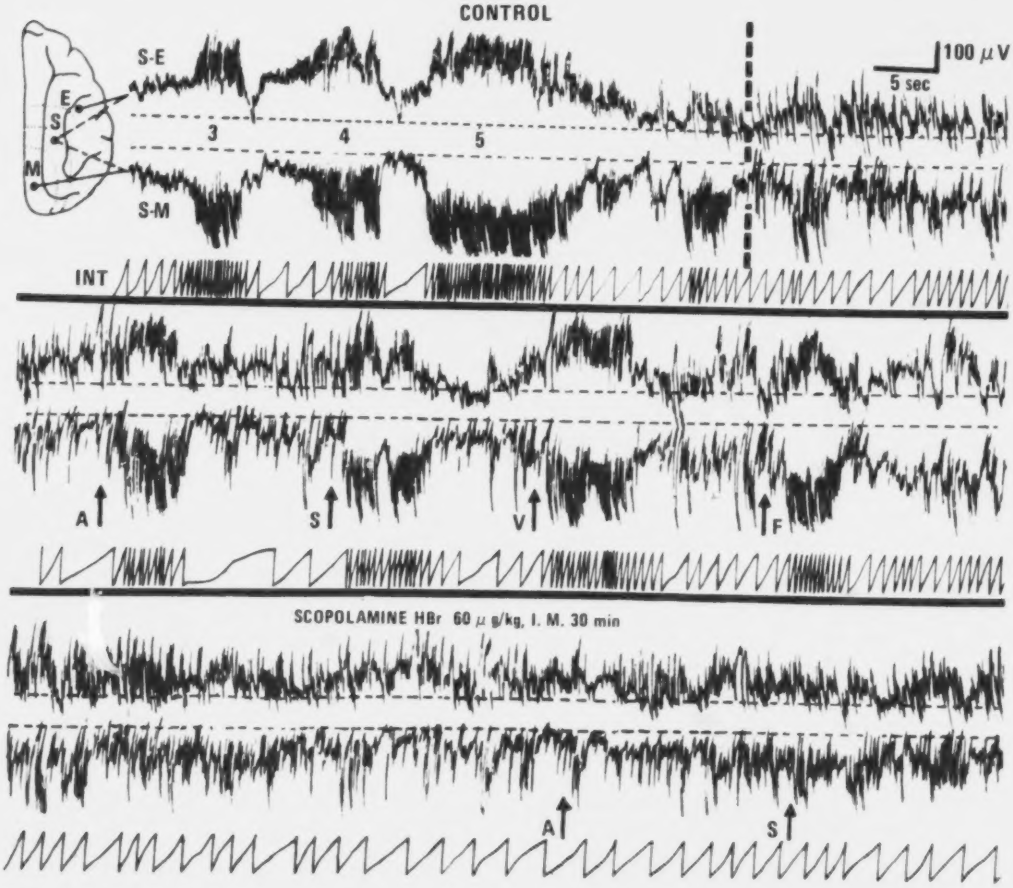

Fig. 1. Typical SOPV responses and K-SPs during slow wave sleep to auditory (A), somatosensory (S), vestibular (V) and flash (F) stimuli (top and middle, respectively). Scopolamine hydrobromide blocks these responses (bottom). For further explanations, see text.

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II. MOTOR CONTROL

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THE PRESENT STATE OF BRAIN MACROPOTENTIALS IN MOTOR CONTROL RESEARCH - A SUMMARY OF ISSUES

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The following section is based on preconference correspondence and on the Motor Control plenary session. The objectives of this section are to analyze and evaluate the contributions of macropotential research to the neuropsychophysiology of movement.

Movements as integral formations

The phenomena encompassed by the term "motor control" are very broad. The neurologist, neurophysiologist, neuroanatomist, neurochemist, experimental psychologist, ethologist, and cybernetician are in one way or another studying the organization of movement, its various components, executive organs, and spatiotemporal relationships. Is there need for yet another approach to the study of motor control processes?

There is a vast experimental literature characterizing the electrical activity of single motor units and muscle discharge patterns. Bernstein (1967) has observed, however, that unit discharge patterns are far removed from movements as integral formations. The limits of most techniques, such as electrical stimulation, used to study movement have been pointed out. For example, Phillips (1966) remarks that electrical stimulation does not evoke the natural functioning of cortex and that movements are intracerebral processes which are not simply equated with the contraction of muscles. Although there is increasing realization that movements are "integral formations" which require conceptualization in terms of intracerebral processes, it is less clearly understood that such processes extend beyond the realm of local brain architectonics. The concept of movement introduces the need to think in terms of higher levels of organization than hitherto accepted forms of anatomical and physiological evidence permit.

Mountcastle et al. (1975) summarized the problem: "Some of our observations suggest that another mode of organization is from time to time superimposed on the basically columnar pattern and that this additional set formation is dynamic and conditional in nature." The study of such dynamic and conditional sets has hitherto been the province of psychological research. McKay (1966), however, has pointed out that "the entities and paths of the psychologist's models have classically had few pretentions to anatomical significance, while those of the physiologist, for reasons of sheer complexity, have been correspondingly vague in their predictions of gross human behavior." Macropotential research could supplement classical methods by offering neurophysiological insight and precision to those dynamic and conditional intracerebral processes which underlie the highly integrated units of behavior and internal processing known as movements.

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Movement-related brain macropotentials

Electrical brain activities generally referred to as motor-related potentials include sustained and phasic changes time-locked to self-initiated actions or to actions triggered externally with or without forewarning. Signal averaging techniques have been widely used to study the Bereitschaftspotential (BP) and CNV, although this technique has diverted interest from movement-related brain macropotentials (MRBMs) which can be observed in scalp recordings without averaging. The mu rhythm (Gastaut 1952, Chatrian et al. 1959) is an example of such an event.

Fig. 1 illustrates corticographic analogs of the mu rhythm recorded from sensorimotor cortex. Note that sensorimotor response is maximal contralateral to the active hand, while occipital rhythms are not altered by movement. The sensorimotor response is less with ipsilateral or sustained contralateral clenching. These observations suggest both topographical and situational specificity of intrinsic sensorimotor rhythms. The significance of this specificity and its relationship to other macropotentials occurring simultaneously are important questions for future research.

The study of evoked potentials while the organism remains in a passive state may also contribute to our understanding of the organization of movement. Dubrovsky (this section) discusses the significance of

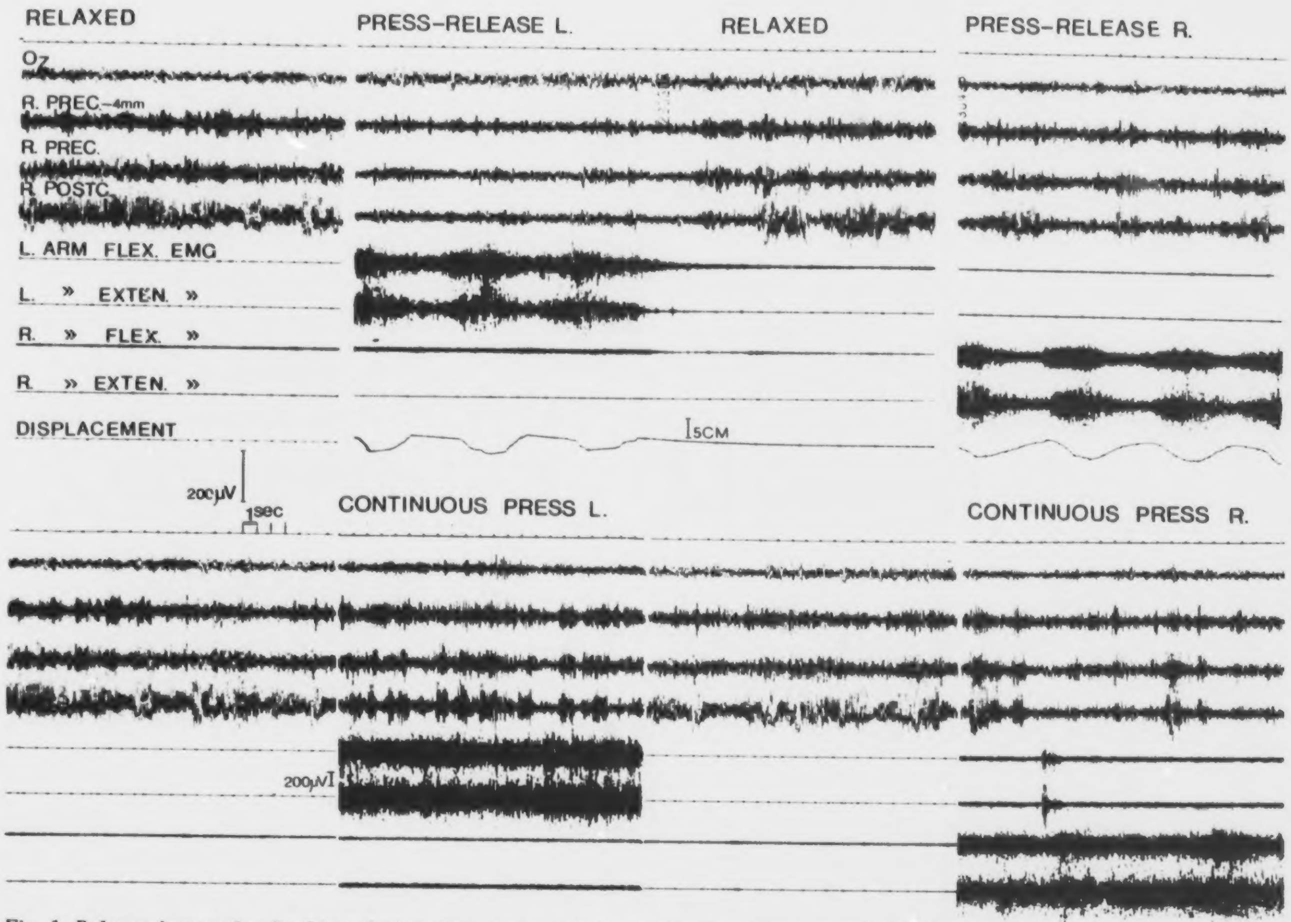

Fig. 1. Polygraph records of subject during alternating periods of relaxation (eyes closed) and fist clenching (left then right). Upper traces illustrate brief clenching and releasing of fist, while lower traces illustrate continuous clenching. Recorded parameters include time, in seconds (chan. 1), scalp EEG (Oz, chan. 2), electrocorticograms from right sensorimotor areas (chans. 3-5), EMG from the left and right forearm flexors and extensors (chans. 6-9), and output of a movement transducer connected to the index finger (chan. 10). R.PREC.-4mm: a gold subdural electrode 4 mm anterior to the right precentral electrode (R.PREC.). Precentral and postcentral (R.POSTC.) electrode sites were identified by recording the characteristic reversed polarity and time shift of the first component of the somatosensory response elicited electrically by stimulation of the left median nerve of the wrist. The reference for scalp and cortical electrodes was an average reference obtained from 64 other gold electrodes implanted in frontal white matter of the patient.

visual and cutaneous input to the cortex. Investigations of somatosensory evoked potentials, furthermore, have suggested specific sensory input to precentral cortex (Papakostopoulos et al. 1974a, 1975; Papakostopoulos and Crow, in press). Further evidence concerning afferent pathways to the motor cortex is contained in neurophysiological (Murphy et al. 1975) and neuroanatomical (Kalil, this section) studies.

Three factors must be taken into account in any attempt to classify movement-related brain macropotentials. The first is the polymorphism of macropotentials which can be recorded from the same cortical area during the same period of time. The second factor relates to the spatial properties of specific components. The third factor concerns the temporal sequence of movement and associated macropotential patterns. Macropotentials tend to convey a deceptive static picture of the brain during the organization and execution of movement unless the temporal sequence of motor and electrical events is carefully defined.

These factors have been taken into account in the following classification of movement-related brain macropotentials.

1. *Resting potentials* – potentials related with the state of the motor system at rest (e.g., sensorimotor rhythm and somatosensory evoked potential).
2. *Preparatory potentials* – potentials related with functions during the preparatory period (e.g., BP and CNV).
3. *Initiation potentials* – potentials related with the initiation period (e.g., motor potential).
4. *Movement execution potentials* – potentials related with the execution of the movement (e.g., N2 or motor cortex potential).
5. *Termination potentials* – potentials related with the termination of the movement (e.g., P2 and skilled performance positivity).

Serial ordering in movement forms the basis of this taxonomy which may be viewed as a five-interval time scale. This classification system has the advantage of accommodating the fragmented data derived from movement-related macropotential studies as well as facts and theories about motor control derived from other disciplines.

Factors such as spatial coordination, target determination, holding, and achievement must also be considered during the unequal intervals of this time sequence. At any point in the sequence of operations involved in any motor act, different parts of the body are subject to different postural states and displacement forces according to the nature or target of the movement. Brain macropotentials could reflect any one or combination of these factors.

Functional issues

Three questions arise with regard to the nature and significance of changes occurring during each time interval. First, do the macropotential changes reflect factors related to movement alone, or do other nonmotoric factors contribute? Second, to what extent do peripheral and central changes involved in every stage of movement influence the macropotential in progress? Third, to what extent do movements influence the sensitivity or selectivity of the organism toward environmental changes, and what are the associated effects on brain macropotentials?

The first question, raised briefly by Cohen during discussion, can easily diverge to a semantic argument of what constitutes a motor act. On the other hand, this issue underlies the venerable controversy whether the CNV and BP are functionally equivalent (cf. McCallum, this section). The excitability of the spinal monosynaptic reflex, for example, increases during the CNV interstimulus interval in the absence of any overt behavior or EMG activity (Papakostopoulos and Cooper 1973).

This evidence indicates involvement of motor structures during the preparatory process but does not help to differentiate the task-specific operations which take place during preparation. There is evidence (Papakostopoulos, this section) that the context within which similar motor actions are executed is reflected in the amplitude and waveform of event-related macropotentials. The evidence suggests that preparation involves motor structures, even at the spinal cord level, and that cognitive or contextual elements of action are reflected in macropotential configurations.

It is probably as misleading to attempt to distinguish a particular movement from the purpose for which it has been organized as it is to suggest a clear-cut separation of sensory and motor elements within the nervous system. Magendie pointed out in 1824 that the separation of nerves of feeling and nerves of motion is arbitrary and of no practical value.

The second question, relating to feedback, was discussed with reference to the motor potential (MP) of Kornhuber and Deecke (1965), the N2 component of Gilden et al. (1966) and Vaughan et al. (1968), and the positivities which follow it known as reafferent potentials (Vaughan et al. 1968, Deecke et al. 1969). The first two terms are generally considered to be interchangeable (cf. McAdam 1973 and Buser 1976). However, Deecke made explicit the position of the Ulm group that the MP is not equivalent to N2. Deecke described the MP as an additional negativity appearing at the precentral cortex contralateral to the moving finger 54 msec before EMG onset. This component is superimposed on an already asymmetrical

BP. The problem is how to distinguish between the two entities if the BP itself is asymmetrical.

An alternative hypothesis is that the N2 component is an index of reafferent activities (Papakostopoulos et al. 1974a, 1975). Evidence of specific sensory input to precentral cortex has been found in man (Goldring and Ratcheson 1972) and animal (Kalil, this section). The results of Gerbrandt et al. (1973) and Papakostopoulos et al. (1975) indicate, furthermore, that N2 follows movement onset. This evidence supports a reafferent view of the N2 component.

In discussing macropotentials associated with afferent input to the cortex, account must be taken of the state of the nervous sytem preceding input. For instance, the configuration of a sensory evoked response differs when a subject passively receives a stimulus compared to when the subject is triggered to action by the stimulus or when the stimulus occurs as a result of motor action by the subject. Precentral and postcentral cortical areas process afferent input in different modes, depending on the motor contingencies of the situation. Hazemann (this section) reviews evidence concerning the effect of movement on sensory evoked potentials.

Vaughan et al. (1968) and Deecke et al. (1969, 1976) suggested that the positive potentials which follow N2 reflect response reafferent activity. The response reafferent hypothesis, however, is not consistent with the results of several studies reported in this section (see Abraham et al., Delaunoy et al., Otto et al., and Papakostopoulos) which suggest that these potentials could reflect neurophysiological concomitants of internal afferent feedback or efferent feed forward processes, possibilities which require experimental verification.

Another related issue is the homogeneity of post-movement positivities and other late positive components described in the ERP literature. For example, is the P300 functionally related to positive potentials associated with visual detection of infrequent events (Cooper et al. 1977) or to skilled performance positivity (Papakostopoulos, this section)?

Theoretical and experimental integration

Kornhuber and his colleagues (Kornhuber 1971; Deecke et al. 1973, 1976) have proposed a comprehensive theory of motor function which integrates data from several disciplines including event-related potential research. According to this theory, preparatory functions are executed prior to movement in several regions of the brain such as the cerebellum, basal ganglia and precentral and parietal cortex. The specific loci involved in preparatory functions vary with the type of anticipated movement. This theory provides an excellent example of how macropotential research can contribute to clinical knowledge and stimulate further experimentation in the area of motor control.

Another approach seeks to integrate data from the central, peripheral, and autonomic nervous systems during the preparation for and execution of movement. This approach, exemplified by the work of Lacey and Lacey (1970), Ingvar (1977), McCallum et al. (1973, 1976), Cooper et al. (1975), and Papakostopoulos and Cooper (1973, 1976, this section), is more experimental than theoretical, but has also contributed substantially to the understanding of motor control processes. These investigators have studied changes in cortical O_2a, heart rate, and spinal reflexes during specific phases of movement.

Need for technological and conceptual innovation

Three methodological issues were discussed: (1) the effect of experimental artifacts on the reliability of data; (2) the need to study integrated motor sequences in place of isolated, purposeless actions; and (3) the limits imposed by current technology.

Extracranial artifacts such as the large electrical potentials generated by eye movements (rotation of the corneofundal dipole) pose serious problems in most areas of ERP research including motor control. Despite the ubiquity of the problem and the keen awareness of most investigators, no foolproof method has yet been devised to entirely eliminate eye-movement artifact from ERP recordings in all subjects. Rosen (this section) presents disquieting evidence from corticographic recordings in monkeys that oculomotor processes associated with saccadic eye movements may significantly alter cortical evoked potentials even when the eye is fixated. The contribution of frontal eye fields to and the effects of different oculomotor control strategies on ERPs require further study.

The reports of McCallum and Papakostopoulos (this section) illustrate the need for refinement of experimental procedures. Both experiments demonstrated that the amplitude and spatial distribution of the CNV and BP were task dependent. Task demands were found to be a more important determinant of macropotential configuration than were individual or group stereotypes. Individual differences do exist, as discussed by Deecke et al. (1976 and this section), but the present data suggest that such differences will be more effectively revealed in experiments which involve complex patterns of interaction with the environment where the pattern of response is flexible rather than stereotyped.

Naturally, such developments will make increased demands on technology in order to study the neurophysiological substrate of complex, integrated movement. Otherwise, we will be limited to the study of simple, stereotyped responses. Improved technology will not only provide stronger evidence for the existing range of phenomena, but will reveal more clearly where fundamental discrepancies exist. For example, Gerbrandt's attempt (this volume) to determine the smallest number of scalp electrodes necessary to study motor processes revealed problems in previous conceptualization of potentials related to self-paced movements. His data suggest that the BP is far from being a unitary phenomenon and that its waveform varies with time in different ways for different areas.

Such approaches underline the complexity of the issues we face and challenge our traditional methodologies. Although there may be agreement that the BP is a preparatory potential, one is obliged to ask how many types or variants of preparation exist. We are only at the threshold of a constructive neurophysiological analysis of preparatory processes and ideational components of movement organization in man. The solution probably lies in understanding the spatiotemporal organization of macrostates. The number of macrostates that can be seen with macroelectrodes will be determined by the spatial constant (i.e., the degree of attenuation over distance) of the brain which is yet unknown for cortical or scalp recordings. (Methodological details and problems of spatial averaging are discussed extensively in Section IX). Perhaps spatial sampling techniques already within the bounds of our technology will enable us to elucidate what Katchalsky et al. (1974) have called the dynamic pattern of brain macrostates.

SPINAL CORD STIMULATION AND EVENT-RELATED POTENTIALS[1]

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Cook (1976) reported insertion of electrodes percutaneously in the thoracic epidural space of the spinal canal in 185 patients with multiple sclerosis (MS). Following a period of continuous inductively coupled electrical stimulation, 69 patients showed significant improvement in some neurological function such as speech, bladder function, or locomotor performance. Electrodes were implanted permanently in these patients and stimulation was maintained; improvement persisted in 51 cases.

The mechanism by which electrical activity induces this benefit is unknown. Symptomatic improvement could be the direct consequence of electrical stimulation of nonspecific projection systems of the brain via the midbrain reticular formation. If so, evoked and slow potential changes might provide useful measures from which to infer the underlying neurophysiological mechanism. McCallum et al. (1973), for instance, found that the shape and duration of SP changes recorded from intracerebral MRF electrodes in humans closely resembled the vertex contingent negative variation (CNV).

Improvement might also be a secondary effect of the emotional impact of the implantation and stimulation procedure. The drama of surgery and experimentation, the novelty of the techniques, the use of an electronic device, the encouragement of well-wishers, and the new-found hope of relief from the distressing symptoms of progressive disease may all play a part. If recovery is dependent on a novel state of sustained excitement, it should be reflected in a postoperative change–presumably an enhancement–in CNV amplitude, at least when the apparatus is switched on and the patient is aware of it.

Methods

Subjects

This preliminary report concerns data obtained from limited experimentation with five patients who had spinal electrodes temporarily implanted. Three patients (RW, CJP, and DHS), aged 34, 36, and 41, were male and two (SE and EFM), aged 43 and 23, were female. Four had multiple sclerosis and the fifth, RW, had motor neurone disease. Lesions were judged clinically to be infratentorial in all patients. In some cases, the nature and severity of the lesions were demonstrated by H-reflex recovery curves and auditory evoked response recording. Detailed clinical and physiological information concerning these patients appears in Illis et al. (1976).

Surgical procedures and results

Two electrodes were inserted under X-ray control in the midthoracic region one or two vertebral widths apart on the dura surrounding the spinal cord. Electrodes were made of insulated steel with exposed platinum tips. A battery-operated stimulator/transmitter at the patient's side generated 100-μsec pulses at a rate of 30 to 40/sec. A receiver located on the skin surface was attached to the opposite end of the electrodes. The voltage of the pulses could be controlled by the patient.

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[1] This work was carried out with the support of the Army Department, Ministry of Defense (British).

At normal stimulation levels, the patients reported paraesthesia throughout the body up to the dermatome level corresponding to the site of the electrodes. In view of the electrode positions adjacent to the dorsum of the dura, it is probable that the dorsal columns were principally stimulated. Increasing voltage could induce a painful sensation and muscle fasciculation, suggesting that stimulation was not confined to the dorsal columns, at least at high voltage levels.

After a day of continuous stimulation, improvement in function was clinically discernible. Improvement continued with further stimulation over the next 2 to 7 days, involving extensive areas of the body and additional functions. Patients also consistently reported a carry-over effect, i.e., they continued to feel benefit hours after prolonged stimulation ceased. Clinical and physiological change are detailed in Illis et al. (1976).

Experiment I

To gain insight into the mechanism by which electrical activity induces the benefits reported and to evaluate the utility of evoked-response techniques for such an application, CNV was recorded both pre- and postoperatively. Postoperative recordings were obtained under both stimulator-on and stimulator-off conditions. Ag/AgCl electrodes were employed at Fpz, Fz, Cz, and Pz, with linked earlobes as reference. The Cz derivation was compensated for eye movements as described by McCallum and Walter (1968). Skin sites were abraded with a blunt needle, giving an impedance of less than 1 k-ohm. EEG was recorded with a 10-sec time constant. Subjects were seated in a large, quiet, darkened room kept at a comfortable temperature. In view of the carry-over effect mentioned above, subjects were asked to switch off the stimulator 15 hours prior to postoperative recording; three of them did so.

Experimental paradigm

A simple CNV paradigm consisting of a distinct warning click through earphones followed 1 sec later by a train of light flashes (16/sec) from a stroboscope 25 cm in front of the subject was employed. Subjects were instructed to terminate the flashes as quickly as possible by pressing a button. The intertrial interval varied irregularly between 5 and 15 sec. Performance was encouraged during short pauses between blocks of 12 trials. Eight blocks were presented in the following sequence: three acquisition, two distraction, one resolution, and two with eyes open and fixated on the pupil reflected in a mirror attached to the stroboscope. During the first six blocks, subjects were instructed to keep their eyes closed and still. CNVs were derived (using a PDP 12) from averages of 8 of the 12 most artifact-free trials. Baseline was computed from mean EEG activity during the 2.1-sec epoch preceding S1, and amplitude from the 200-msec epoch preceding S2.

Distraction trials were included in order to evaluate the possible distracting effect of electrical stimulation (McCallum and Walter 1968). An intermittent tone was presented through the earphones between trials during this phase.

Results

Recordings made prior to electrode implantation showed the form, amplitude, distribution of CNV components, and effect of distraction to be similar to those found in healthy subjects. Mean drop in Cz amplitude during distraction compared to acquisition was 7 μV(standard deviation = 3.9).

Averages of pre- and postoperative vertex CNVs are shown in Fig. 1. Waveforms are indistinguishable except for a slight increase in postimperative negativity and a slight increase in the P300 component after surgery. There was no consistent change in the P300 component, and 75% of the difference was derived from one subject (RW). Postoperative CNVs with the stimulator on and off are compared in Fig. 2. Even less difference is apparent between these two average waveforms. Neither pre- nor postoperatively were there large individual differences that might be concealed by averaging. The largest difference was a 5-uV increase in amplitude after surgery in the case of EFM, who failed to benefit from the procedure. The mean computed difference in maximal pre-S2 CNV amplitudes in both Fig. 1 and 2 was 1 μV. The effect of distraction after surgery, with or without the stimulator, was essentially the same as before (6 μV, SD=3.9).

Discussion

The absence of any difference between CNVs with the stimulator on or off could be explained by a balance between the stimulator's distraction (CNV reducing) and stimulation (CNV enhancing) effects. On the other hand, the experience of other CNV experimenters that a continuous stimulus that does not intrude on the subject's awareness does not have a CNV-reducing effect suggests that there was no distraction effect and no compensating CNV enhancement.

It had also been suggested that the drama of the operation and experimentation and the hope of beneficial treatment might be reflected in a postoperative increase in CNV in either the stimulator-off or the stimulator-on conditions. The absence of any substantial change suggests that the benefit derived from stimulation was not a placebo effect dependent on the general excitement of the patient. However, it is possible that the subjects were so highly motivated that no further increase in CNV was possible (ceiling

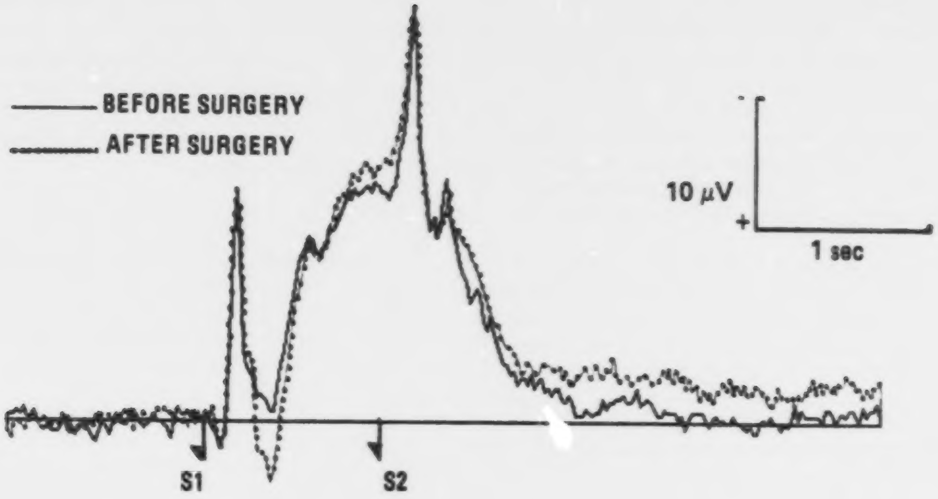

Fig. 1. Combined average of CNVs from five subjects after surgery compared with CNVs from the same subjects before surgery. (Each trace is derived from 320 trials.)

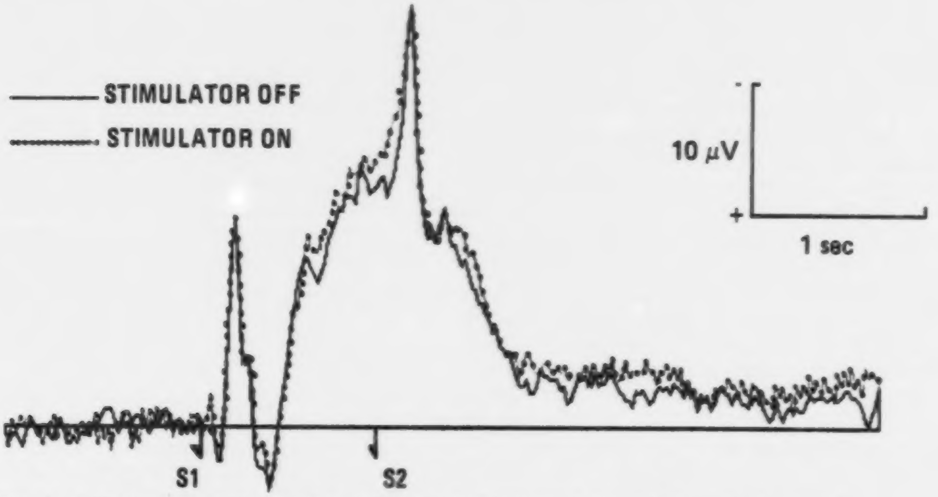

Fig. 2. Combined average of CNVs from five subjects receiving spinal cord stimulation compared with CNVs from the same subjects not receiving stimulation. (Each trace is derived from 160 trials.)

hypothesis, Knott and Irwin 1973). The brief opportunity available for experimentation did not permit the rejection of this hypothesis until later (Abraham et al. 1978).

It appears possible that the impulses, although not susceptible to end-organ habituation or peripheral inhibition since they were generated by a stimulator in the spinal cord, did not reach the cortex in sufficient strength to affect the CNV. It also appears possible, if CNV generation has a primary subthalamic source (McCallum et al. 1973), that the spinal cord stimulator, in activating the dorsal columnar pathway which has few collaterals to the reticular formation, could virtually bypass the midbrain reticular formation and thus have minimal influence on the CNV. An additional experiment was carried out to evaluate these possibilities.

Experiment II

The four multiple sclerosis patients took part in this experiment. A mechanical vibrator was strapped to the skin overlying the lower end of the right kidney. The purpose of this was to provide a stimulus comparable to that which the electrical stimulator was supposed to generate. The kidney site was chosen so that it did not cause discomfort to the seated patient, who could nevertheless feel the vibrator when it was switched on in spite of loss of sensation in other areas. The patient could not see or hear the vibrator, since the sound was effectively masked by 70 dB white noise transmitted through earphones. The current in the vibrator was adjusted to induce the minimum possible vibration when the circuit was closed. The patient then adjusted the voltage of the spinal cord stimulator so that both pieces of apparatus delivered sensations of roughly equivalent intensity. This generally involved a reduction in stimulator voltage and an accompanying reduction of the paraesthesiae, sometimes to a band around the chest. The current to vibrator and stimulator was controlled by a PDP 12 computer which delivered a 250-msec burst of stimulation via one or the other apparatus. This burst was incorporated into the CNV paradigm, replacing the flashes at S2 for 40 trials and then replacing the click at S1 for 40 trials. The vibrator and stimulator were alternated after each block of 10 trials. Patients' eyes were open and fixed on the mirror throughout this phase of the experiment, and a rest was allowed after every 20 trials.

Results

Vertex CNVs observed during stimulator and vibrator conditions are superimposed in Fig. 3 (S2 substitution) and Fig. 4 (S1 substitution). CNVs recorded in S2 substitution trials differed from Experiment I waveforms only in the marked attenuation of the S2 evoked potential. CNV resolution was equally rapid in both experiments. In the S1 substitution conditions fast and slow evoked potentials appeared earlier and were larger when generated by the stimulator than by the vibrator. The increased magnitude may be an electrical artifact from the stimulator since a sharp rise appeared at S1 onset. The latency difference is attributable to a mechanical delay in vibrator response, a tremor transducer attached to the vibrator indicated a slow rise time to peak.

Discussion

Spinal cord stimulation did not produce any observable change in CNV amplitude or shape in Experiment I. The results of Experiment II rule out the possibility that patients did not perceive spinal cord stimulation since motor responses were performed correctly in both S2 substitution conditions. It should be noted, moreover, that the voltage of the stimulator had to be reduced in Experiment II to match the perceived intensity of the vibrator. Perception of the electrical stimulus should therefore have been more pronounced in Experiment I than in Experiment II. It is improbable that impulses from the stimulator were too weak to affect the CNV.

The apparent differences in evoked and slow potential patterns evoked by electrical and vibratory stimuli in S1 substitution conditions were probably artifactual. The slow mechanical rise time of the vibrator presumably induced a time lag before the stimulus level reached the threshold of the sensory end-organ. Differences in axon length from the sites of vibratory and electrical stimulation cannot account for the observed time lag. If latency and amplitude differences are dismissed as artifact, then one may conclude that comparable CNVs were elicited by both types of warning cues. This finding implies either that the CNV may be initiated by stimulation of the dorsal column-medial lemniscus-specific thalamic nuclei pathway, or that the stimulator activated other pathways.

Conclusions

The absence of pre- and postoperative differences in CNV found in this study contrasts with other physiological findings (Illis et al. 1976). A return toward normal of the H-reflex recovery curve and the fifth component of the auditory evoked response in some patients suggested that physiological change had taken place. Results of these preliminary experiments suggest that the beneficial effects–psychological or physiological–of spinal cord stimulation are not mediated via cortical excitement as measured by the CNV. The data, however, do not preclude the possibility that CNV amplitude reached a ceiling level prior to spinal cord stimulation in highly motivated patients, though subsequent experimentation (Abraham et al. 1978) did so. The similarity of CNV waveforms with and without dorsal column stimulation suggests, moreover, that reafferent activity, presumably mediated by this pathway, does not contribute to the CNV.

Finally, the ability to bypass peripheral nerves and end-organs provided by spinal cord stimulation offers a unique opportunity to those investigating event-related potentials in situations easily confounded by peripheral factors.

Summary

Clinical improvement has been observed in multiple sclerosis patients following spinal cord stimulation, although the mechanism underlying this effect is not known. Two brief CNV experiments were undertaken to investigate possible changes in psychological or neurophysiological state associated with clinical improvement. Spinal cord stimulation did not produce any discernible change in the CNV, suggesting that therapeutic effects are not mediated by cortical mechanisms.

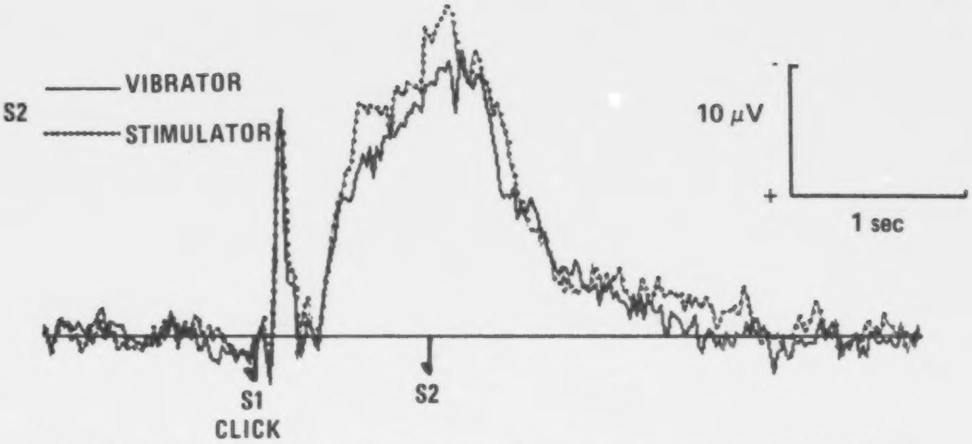

Fig. 3. Combined average of CNVs from three subjects in whom spinal cord stimulation was used as the imperative stimulus compared with CNVs from the same subjects in whom external somatosensory stimulation was used as the imperative stimulus. (Each trace is derived from 48 trials.)

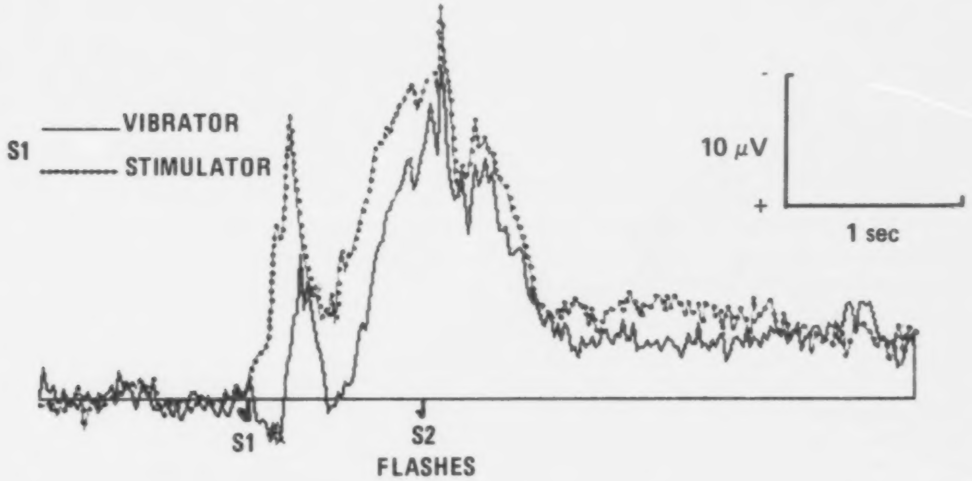

Fig. 4. Combined average of CNVs from three subjects in whom spinal cord stimulation was used as the warning stimulus compared with CNVs from the same subjects in whom external somatosensory stimulation was used as the warning stimulus. (Each trace is derived from 48 trials.)

FUNCTIONAL SIGNIFICANCE OF CEREBRAL POTENTIALS PRECEDING VOLUNTARY MOVEMENT

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It has been established that cerebral activity preceding voluntary self-paced movement (e.g., index finger flexion) can be recorded through the intact human scalp (Kornhuber and Deecke 1964, 1965). Three different potentials occur: a slow potential, called the Bereitschaftspotential (BP) or readiness potential, and two faster potentials, referred to as the premotion positivity (PMP), and the motor potential (MP). Certain methodological requirements are necessary to record these three potentials. Amplifiers with long time constants are necessary to record BP. To pick up the faster potentials and to achieve the necessary signal-to-noise ratio, exact temporal triggering conditions and a large number of trials are required. Best results are obtained if the subject is trained to relax the agonist muscle to the extent of complete silence in the intramuscular electromyogram (EMG) and then perform an abrupt and rapid movement. A sensitive triggering level must be used to ensure triggering from the very first intramuscular action potential. Deecke et al. (1976) have shown with index finger flexion that the earliest activity occurs in the agonist muscle (*M. flexor digitorum communis, pars indicis*), although accompanying muscular activity is recorded in many other arm and neck muscles. Additional methodological requirements are the exclusion of eye movements (e.g., by gaze fixation) and careful editing of every trial.

If these precautions are taken, three different types of subjects are found (Fig. 1). Type A (15%) shows increasing negativity until movement onset in all precentral and parietal leads with a steep rise about 60 msec prior to EMG onset in the contralateral precentral lead. Type B (41%) shows increasing negativity until movement onset in the contralateral precentral lead but a positive deflection about 90 msec prior to movement onset in other precentral and parietal leads. Type C (44%) shows a positive deflection in all precentral and parietal leads, but a less steep slope in the contralateral precentral lead. Both Type B and Type C (85%) exhibit PMP. Fig. 1 illustrates that, in the final 150 msec prior to EMG onset, the waveform is complicated by the superimposition of the three potentials mentioned above, differing in polarity and topographical distribution and perhaps morphology between subjects.

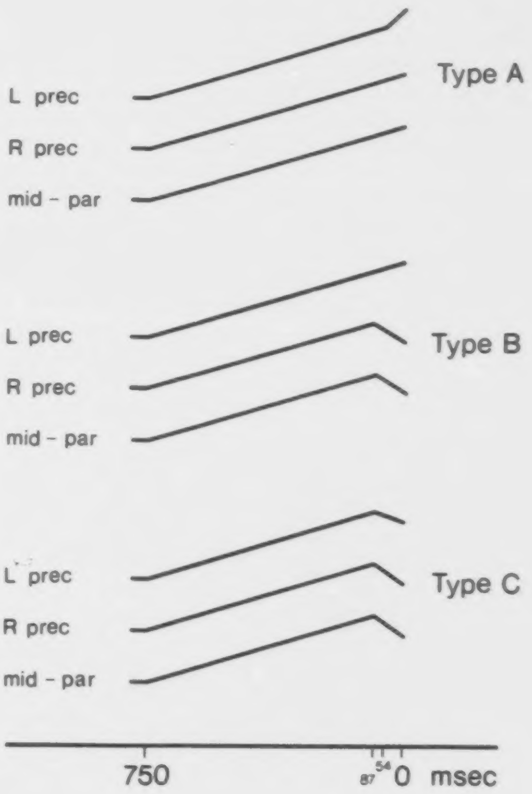

Fig. 1. Three different types of subjects. Schematic diagram of the potential course in left and right precentral and midparietal leads preceding right-sided finger movement. (Deecke et al., 1976).

Bereitschaftspotential

The slow premovement potential (Bereitschaftspotential, readiness potential, or N1) is a negative shift of the cortical dc potential, as is the contingent negative variation (CNV). The principal characteristics of BP are early onset (commencing up to 1.5 sec or more–mean 0.8 sec–before movement), gradual negative increase, and bilateral distribution over the parietal and precentral cortex of the two hemispheres. The BP is bilateral–even if the movement is only unilateral. These characteristics suggest that the early BP cannot reflect motor command processes, since a potential reflecting motor command would have to be faster than motor reaction time. The term *early preparatory process* is suggested for BP, meaning a thalamocortical facilitation process which selectively excites those cortical areas involved in the intended movement and inhibits or does not affect other areas. A negative shift of cortical dc potential is caused by an increase in synaptic drive in (upper) cortical layers, since intracellular recordings of cortical neurons reveal a simultaneous decrease of membrane potential and an increase in excitatory postsynaptic potential (EPSP) rate (Caspers and Speckmann, in press). The early preparatory process of the BP does not reflect simply general arousal because it can be modified by the experimental situation. The BP is, therefore, a valuable indicator for the loci of cortical activity or inactivity.

The literature concerning BP laterality is controversial. The CNV appears to be symmetrical even in split brain patients responding with their right hand to stimuli flashed into their right visual field (Gazzaniga and Hillyard 1973). Lateralization of the CNV has been observed only when higher lateralized cortical functions such as speech (Low et al. 1976) or numeric operations (Butler and Glass 1974) are addressed in the experimental situation. When we first recorded the brain activity preceding voluntary movement (Kornhuber and Deecke 1964), we expected that a unilateral movement would be preceded by unilateral (i.e., contralateral) cortical activity as suggested by classical concepts based on stimulation of the motor cortex. Finding a bilateral negativity preceding unilateral movement was, therefore, a surprise. Bilaterality does not necessarily imply bilateral symmetry, but this was the case in the initial part of the readiness potential shown in bipolar recordings of left vs right precentral and left vs right parietal leads. Only precentrally did a slight contralateral preponderance occur, commencing about 400 msec prior to EMG onset and averaging 0.9 μV at a time 150 msec prior to movement.

In order to extract the three different potentials, superimposed on each other in the final 150 msec prior to EMG onset, certain measurement rules were established (Fig. 2). BP was measured 150 msec prior to EMG onset to avoid contamination by other potentials. The contralateral precentral preponderance is equivalent to Gerbrandt's (1977) asymmetrical N1 component. Parietally, however, the BP is absolutely symmetrical 150 msec before EMG onset (Fig. 3). In conclusion, whether the BP is symmetrical or lateralized depends on the location and time of measurement. Fig. 3, a three dimensional plot of averages from 39 subjects, illustrates BP lateralization.

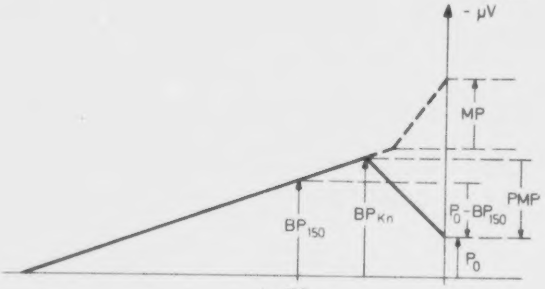

Fig. 2. Rules for measuring the three different potentials. The Bereitschaftspotential (BP) is measured (with respect to a prepotential baseline) 150 msec prior to EMG onset (BP_{150}) and at its kinking (if present) to positivity (BP_{kn}); P_o is the amplitude at EMG onset. For measurements of the premotion positivity (PMP), two differences were taken: P_o-BP_{150}, possible in all the graphs and P_o-BP_{kn} (PMP proper), only possible in graphs with a kink. The motor potential (MP)–dotted line–was measured in bipolar recordings, contralateral vs ipsilateral precentral or contralateral precental vs midparietal, to extract the two bilateral potentials, BP and PMP. The MP represents the additional negativity over the contralateral motor cortex, which occurs on average 54 msec before EMG onset (Deecke et al., 1976.)

The precentral contralateral preponderance of the BP and the MP correlates with handedness (Deecke et. al. 1973). Twenty-five right-handed subjects showed significantly more negativity (2 $p<.05$) recorded over the dominant motor cortex than the minor one, both being contralateral to the movement. In 13 left-handed subjects, an analogous trend (not statistically significant) toward lateralization was observed, in accord with sinistrals being more ambidextrous (less cortically lateralized) than right-handed subjects. Similar results were obtained by Kutas and Donchin (1974). The BP is subject to psychological factors including motivation, and gradually declines with age beyond the fourth decade of life (Deecke et al., this volume).

Premotion Positivity

In Type B and C subjects (85% of the test population), a positive deflection (premotion positivity, PMP, or P1) was observed in the final 150 msec prior to EMG onset. PMP was maximum over the anterior

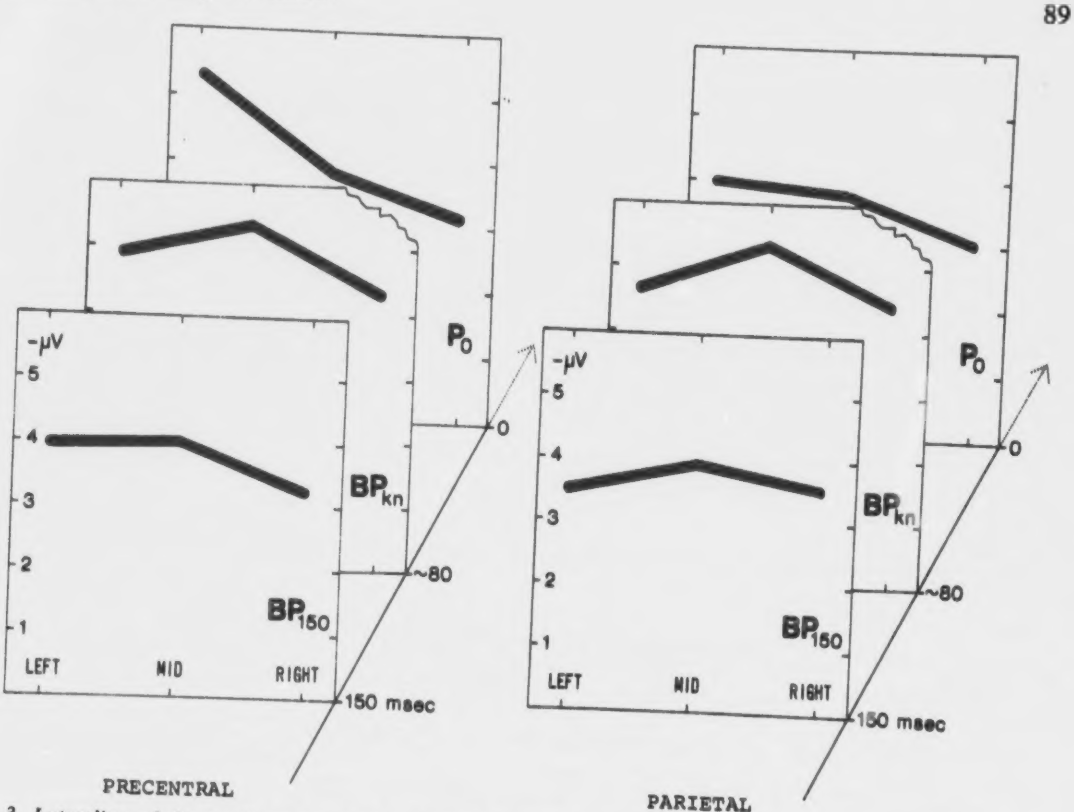

Fig. 3. Laterality of the readiness potential. Three-dimensional plot of the distribution of negativity preceding right-sided finger movement (grand averages across 39 subjects). X-axis: electrode positions over the left, mid, and right precentral and parietal regions. Y-axis: negativity in microvolts. Z-axis: time prior to EMG onset. In precentral leads (left subfigure), the BP is slightly lateralized (contralateral preponderance at BP_{150} and BP_{kn}). At P_o, pronounced lateralization due to motor potential is seen. In parietal leads (right subfigure), the BP is exactly bilaterally symmetrical (BP_{150} and BP_{kn}). The slight (insignificant) lateralization at P_o may be due to spread of the motor potential.

parietal region, Pz (cf. Fig. 1 in Deecke et al., this volume). PMP was measured as the difference P_o-BP_{kn} or P_o-BP_{150} (Fig. 2). Since the mean onset time of PMP is 87 msec prior to EMG onset, which is shorter than mean motor reaction time, this potential might reflect cerebral activity associated with the motor command.

The PMP has also been described by Vaughan et al. (1968), Shibasaki and Kato (1975), and Gerbrandt (1977). At present, there seems to be agreement about PMP phenomenology, but major controversy about its functional significance. The Ulm group considers the PMP to be an expression of movement initiation or motor command, which originates in the parietal area. Vaughan et al. (1970) suggested that the PMP is associated with pyramidal tract activity. Shibaski and Kato (1975) proposed that the PMP is the expression of unilateral inhibition, unilateral movement being the result of unilaterally inhibited bilateral movement. Gerbrandt (1977) has confirmed the existence of the PMP, but speculates that it may be an epiphenomenon of movement occurring toward the end of long experiments. The Ulm group demonstrated at Bristol (McCallum and Knott 1976), however, that the PMP can be seen after the first few trials (Fig. 4). The reason for the variable appearance of the PMP in subjects is not known (see discussion above of different types of subjects), but we have found that a subject maintains his type in repeated experiments, i.e., there is high intra-subject constancy of the PMP.

The hypothesis that the PMP reflects a motor command from the parietal cortex is supported by several considerations: (1) The PMP is not simply the resolution of the BP since there is no correlation between PMP and BP amplitudes (Deecke et al. 1976). (2) The PMP preceding tactually guided finger movements is maximal over the anterior parietal region of area 5, which is the sensory association cortex of the somatosensory modality. The parietal area, whose destruction causes apraxia, is classically considered to be the key structure for learned tactually guided movement and skills. The PMP may, therefore, re-

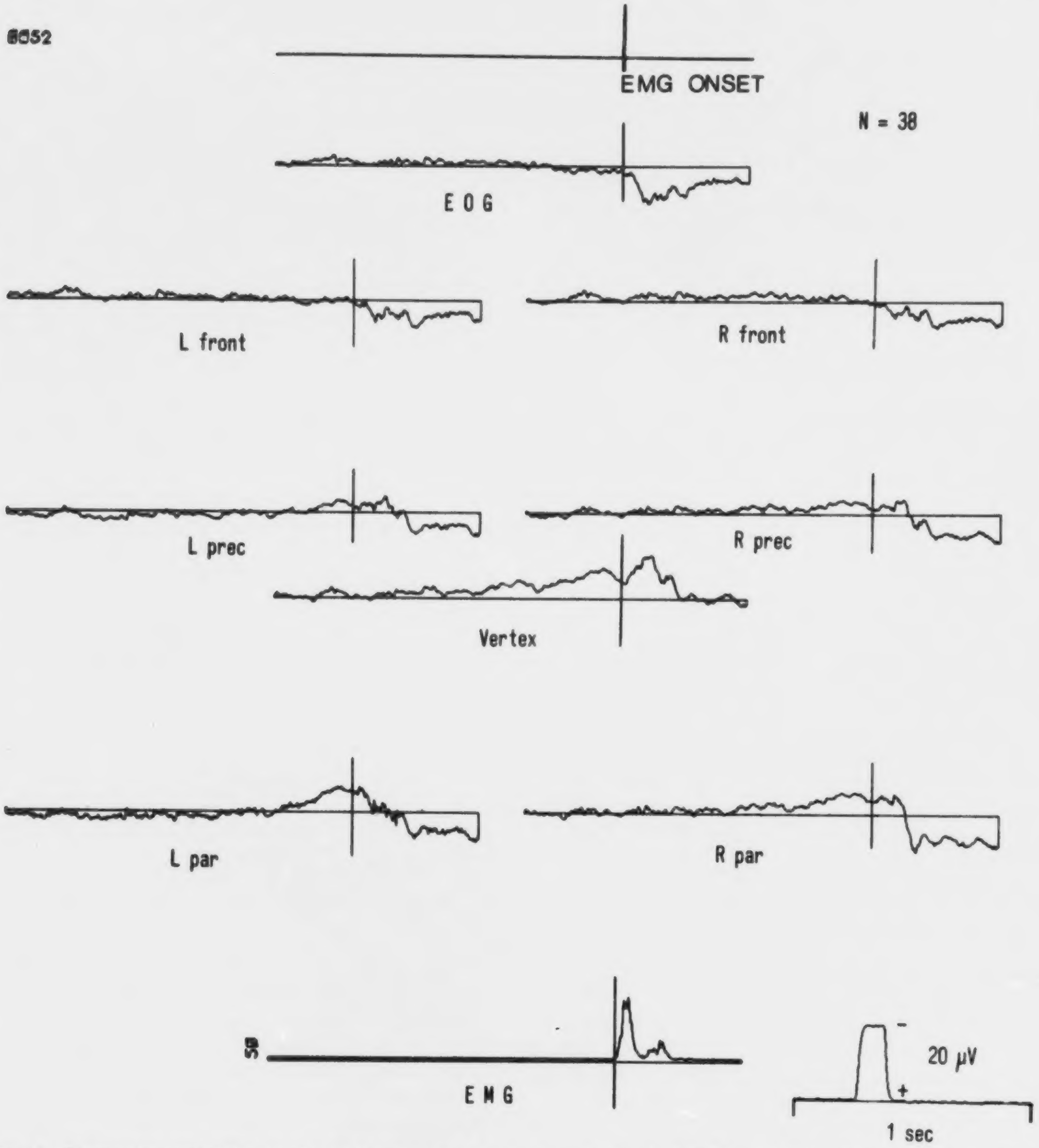

Fig. 4. Premotion positivity in the beginning of an experiment. Typical PMP preceding right-sided finger movement, which is discernible here after 38 trials. Maximum at the vertex.

flect the activation of a movement program stored in the parietal cortex. This spatial code must then be converted to temporal code for the exact timing of movement parameters. According to the theory of Kornhuber (1971, 1974), conversion is achieved by subcortical motor function generators of cerebellum (fast, preprogrammed movements) and basal ganglia (slow, smooth movements). (3) The 33-msec difference between PMP and MP mean onset times permits information transfer and processing via a cortico-cerebello-motor cortical loop. (4) Thach (1970) has confirmed in animals that the cerebellum is activated prior to the motor cortex. The onset time of frequency changes in cerebellar dentate cells (70 msec before EMG) would fit well between PMP onset time (87 msec) and MP onset time (54 msec). Thach (1975) reported that neuronal discharge patterns of dentate cells changed significantly earlier than cells in motor cortex (simultaneous recordings in the same animal). In the thalamic relay of the dentato-cortical path (ventrolateral nucleus), activity also changes well in advance of movement onset (Jasper and Bertrand 1966, Evarts 1970). Finally, Mountcastle et al. (1975) have demonstrated that the anterior parietal region contains so-called "command neurons" that are active prior to movement

Motor potential

What we call the motor potential (MP) is the additional negativity that occurs over the contralateral motor cortex immediately prior to EMG onset. Whereas the PMP and BP are bilateral, the MP is the only unilateral potential preceding voluntary movements of one side. A bipolar montage was used to extract this additional negativity from the BP–i.e., contralateral vs ipsilateral precentral and contralateral precentral vs midparietal (Fig.2). A definite upward kinking of the waveform, arising from the slow negative deflection of the contralateral preponderance, was discernible in about 76% of the subjects. Onset of this kink averaged 54 msec prior to the first intramuscular action potential in the agonist muscle.

It is impossible to execute an index finger movement in isolation. There are always accompanying movements in other hand, arm, and even neck muscles. However, it has been shown that with index finger flection the earliest activity occurred in the agonist muscle, from which the trigger pulse was derived (cf. Deecke et al. 1976, Fig. 2B). Thus, we are certain that the motor potential recorded in bipolar leads is a premovement potential.

It should be stressed that the MP is not identical with the monopolarly recorded N2 component, the premovement nature of which has been questioned in epicortical recordings (Papakostopoulos et al. 1974a). Indeed, this component also occurs with passive movements (Kornhuber and Deecke 1965) and shows phase reversal between precentral recordings (negative polarity) and postcentral recordings (positive polarity, cf. Kornhuber and Deecke 1965, Fig.7C). These findings, obtained with subgaleal needle electrodes, have now been confirmed in epicortical recordings by Papakostopoulos et al. (1974a).

Spatial and temporal characteristics of the MP immediately suggest its functional significance: its location is restricted (with unilateral finger movement) to the hand area of the contralateral motor cortex and its onset is very close to EMG onset (54 msec on the average). The MP, therefore, is probably associated with activity of the motor cortex initiating the descending volley in the pyramidal tract. The motor cortex is a highly specialized structure, but by no means the origin of all voluntary movement, as assumed in classical concepts. According to current theory (Kornhuber 1971, 1974), only those movements that require the highly sophisticated tactile analysis provided by the precentral and postcentral gyri have ascended to motor cortex during phylogenesis. Generation of movements which do not require tactile guidance, such as eye movement, remains in subcortical structures. Therefore, no motor potential is found preceding eye movements (Becker et al. 1972). Movements dependent on an intact motor cortex in the primate are fine finger, toe, lip, and tongue movements, and manual skills requiring tactile control. The somatotopic representation of these parts is thus disproportionally large in the motor (and somatosensory) homunculus.

Further experiments with different types of movements are necessary. Movements can differ in purpose, speed, context of action, internal needs, and modality of mediating stimuli, as well as the part of the body involved in movement. The classical assumption that movements originate in motor cortex is therefore false. The motor cortex comes into play later in the course of movement preparation and only with certain movements. The willful initiation of movement can arise in many cortical areas of the so-called "sensory association" fields, depending on the special type of movement: tactually guided movements in the somatosensory association cortex, visually guided movements in the visual association areas, speech movements in the speech centers, writing, music playing, etc., in their respective centers. It appears that the entire cortex has immediate access to movement by means of known omnicortical projections to subcortical motor function generators of the cerebellum and basal ganglia.

Reafferent potentials

This term has been suggested for potentials that occur after movement onset (Kornhuber and Deecke 1965) because the sequence of positive and negative components after EMG onset closely resembles the average evoked potential to somatosensory stimuli. Furthermore, the same components, although somewhat larger in amplitude, occur after passive movements (Kornhuber and Deecke 1965, Papakostopoulos et al. 1975). The functional significance of this potential complex is probably reafferent activity evoked by the movement. Thus, this complex could be called a proprioceptive evoked response. It seems reasonable to assume that reafferent potentials originate mainly from peripheral receptors such as cutaneous, deep somesthetic, and muscle spindle receptors, but may also come from feedback or reentrant activity of lower motor centers in the brain stem, cerebellum, or spinal cord. As a result, the reafferent potentials would not be completely abolished after rhizotomy (Vaughan et al. 1970). The findings of Vaughan et al. are therefore not entirely contrary to the reafferent conception of potentials after movement onset. The notion that passive movements evoke larger potentials than similar active movements is of interest in view of theoretical concepts such as Effernzkopie or corollary discharge (Holst and Mittelstedt 1950).

EXPERIMENTAL MANIPULATION OF MOTOR POSITIVITY: A PILOT STUDY[1]

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The slow positive wave that follows movement onset has generally been attributed to proprioceptive or kinesthetic afference (cf. Kornhuber and Deecke 1965), although this hypothesis has never been confirmed experimentally. Several observations do not support this hypothesis: (1) postresponse positivity persists in monkeys after dorsal rhizotomy (Vaughan et al. 1970), (2) the positivity persists longer (>500 msec) than the predicted duration of proprioceptive discharge, and (3) the waveform is frequently absent in psychopathological patients in whom there is no apparent proprioceptive deficit.

An alternative hypothesis is that postresponse positivity may be analogous to the P300 wave (Sutton et al. 1965) and may reflect the uncertainty or probability of occurrence of the motor act. The present experiment was designed to test this hypothesis.

Method

Three normal adults (two men and one woman, mean age 35 years) were instructed to extend the right forefinger at regular intervals against a given resistance of 50g (R1) or 200g (R2). Each subject completed two sequences of 150 trials each in which R1 (or R2) was presented randomly on 1/3 of the trials. The probabilities were reversed during the second sequence.

EEG was recorded at the vertex with chlorided silver electrodes referred to the left earlobe and with a 5-sec amplifier time constant. EOG was also recorded for rejection of trials with eye movement artifact. Averages were triggered from the response mechanogram. The averaging epoch was 4 sec (1.5 sec before the beginning of movement and 2.5 sec after). Two measurements were made on the averaged waveforms: (1) the readiness potential (RP) computed as the voltage difference between the potential at movement onset defined by mechanogram, and baseline (initial 500 msec of the average) and (2) the positive wave measured as the voltage difference between baseline and the maximum positivity following movement onset.

Results and comments

RP did not vary as a function of anticipated or unexpected resistance. The positive wave did not vary as a function of the expected (2/3) resistance, but was larger for the unexpected (1/3) resistance, irrespective of actual level, in two subjects.

These results provide limited support for the proposed hypothesis that postresponse positivity may be analogous to P300 and may reflect the certainty or probability of a salient feature of the motor act. Perhaps this positivity reflects the operation of a central comparator between a motor program elaborated before movement and a neural representation of the executed movement. Observations in eight additional subjects run under the same experimental conditions confirm the preliminary results reported here.

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TELERECEPTIVE, PROPRIOCEPTIVE, AND CUTANEOUS INFORMATION IN MOTOR CONTROL[1]

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Two broad views can be distinguished in the interpretation of mammalian brains. In one, articulated by Craik (1943), the "fundamental feature of neural machinery" is the "power to parallel or model external events." This model is matched against input from daily life in order to select the most appropriate line of action (Young 1971). In contrast to this perspective which emphasizes perceptual aspects of the central nervous system, other views emphasize motor control as the central determinant in the evolution and function of the brain. This conception can be traced to S. C. Pierce's pragmatic view that "the evolutionary increase in man's capacity for perception, feeling, ideation, imagination, and the like, may be regarded, not so much as an end in itself but as something that has enabled us to behave, to act, more wisely and efficiently" (Sperry 1952). Lashley (1951) encompassed both positions: "the neurological problem is in large part, if not entirely, the translation of the afferent pattern of impulses into the efferent pattern." This review will summarize recent work on the contribution of proprioceptive, telereceptive, and cutaneous stimuli in the development of forces and the spatiotemporal pattern necessary for movements directed toward the outside world.

The distance receptors of vision, audition, and olfaction are axial in the development and construction of the nervous system (Sherrington 1906). Eyes, by signaling distant events, can provide for the planning of behavior–not merely reflex responses, but complex activity in which cortical integration plays a fundamental role. In recent experimental work, the relevance of midbrain structures in visually guided behaviour has been clearly established. Phylogenetic and physiological data, as well as ablation and deprivation experiments, led to the notion that visual localization is primarily associated with activity in the superior colliculus, whereas visual identification involves the geniculostriate pathway (see review in Dubrovsky and Garcia-Rill 1971). It is clear, however, that perception of a single unified object or event includes attributes of quality, intensity, position in space, and duration in time. The integration of the output of parallel channels of intermediate sensory processing is then a necessary condition to the principle of parallel processing (Davis 1956).

Phillips (1966) has advanced the concept that corticofugal neurons in the motor cortex are "common paths" leading out of the cortex where many differentiated peripheral inputs are integrated. Since planning of extrapersonal motor strategies requires a properly defined spatial context, we decided to explore the possibility of convergence and interaction (a prerequisite for integration, Davis 1956) in the motor cortex of two distinct neuronal groups related to visual perception–the superior colliculus and the occipital cortex.

Experiments with anesthetized cats revealed that the motor-sensory cortex receives stimuli both from the visual cortex and from the superior colliculus. Almost half of the 100 cells studied in this cortical zone received convergent stimuli from both central areas. Inhibitory effects, studied by stimulating against a background of activity induced by iontophoretic release of glutamate, were observed in 51% of the neuronal population studied. Analysis of latencies, duration of inhibitory effects, and following frequencies, indicated that the superior colliculus and occipital cortex stimuli arrive at the pericruciate cortex by independent pathways (Dubrovsky and Garcia-Rill 1971).

After establishing that the visual cortex and superior colliculus may mediate visual information reaching motor cortex, the response characteristics of motor-sensory cortex neurons to natural visual stimulation were investigated (Garcia-Rill and Dubrovsky 1971, 1973, 1974). Briefly, responses to stimuli within visual receptive fields were of the "on," "off," and "on-off" type. Most receptive fields were rectangular and very large. About 75% of the 203 neurons studied

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had receptive fields averaging 72° x 83° and impinged on both nasal and temporal regions of the visual field; the rest were limited to the nasal side and averaged 38° x 49°.

Latency of excitatory responses to both the onset and disappearance of stimuli averaged 45 msec. Inhibitory effects analogous to the excitatory activity evoked by discrete retinal stimulation were also found. The latency for inhibitory responses was longer, averaging 75 msec to an "on" stimulus, and 65 msec to an "off" stimulus. A characteristic of the response of motor cortex neurons to visual stimuli was the inability to follow recurrent presentations beyond 1/sec.

A majority of units (56%) having visual receptive fields displayed movement sensitivity. Only 19% of movement-sensitive cells had a preferred direction for visual stimuli.

Finally, in examining the relationship between visual receptive fields and cutaneous receptive fields of the same units, a topographical distribution of visual input to motor-sensory cortex became evident. Essentially, more colonies of cells with input from the trunk received visual information than those colonies with input from the distal forelimbs. Only 15% of cells with exclusive input from the distal extremities received visual input, whereas 75% of neurons with exclusive and convergent input from proximal areas received visual information.

The topographical organization of visual afferents in motor cortex, the large size of visual receptive fields, the long latency of response, and the poor frequency-following characteristics of motor cortex neurons suggest that control of accuracy of movements is not mediated by visual input to motor cortex. The data do suggest, however that visual afferents to motor cortex may be related to spatial aspects of perceptual-motor function. This hypothesis is further supported by the binocular convergence of visual pathways in motor cortex. According to Young (1962), bilateral representation is the basis of "a system for representing features of the environment that are signaled by various receptors in their correct spatial relations."

Although neurons in the motor cortex are characteristically polymodal for cutaneous and deep modality receptors, visual and vestibular afferents (spatial information) converge preferentially onto areas corresponding to the body axis and proximal limb zones. The latter areas are also richly endowed with callosal connections, while areas corresponding to distal extremities are almost devoid of callosal projections (see Garcia-Rill and Dubrovsky 1973). Results reviewed here are also consistent with the differential organization of neural systems controlling axial musculature of the limbs on one side, and distal on the other (Kuypers 1963). These data, clinical observations on the role of vision in postural mechanisms for normal and pathological conditions, and developmental studies emphasize the formation of a body-centered spatial framework as essential conditions for the development of visually guided behavior (Garcia-Rill and Dubrovsky 1974) and suggest that visual afferents arriving at the motor cortex are related to tracking functions involved in defining the spatial context in which movement will take place.

We further proposed that integration of proprioceptive, somatic, spatial, and callosal information converging onto areas of the motor cortex which correspond to the midline of the body is part of a neural process related to construction of a reference axis for limb movement. This axis would form part of a system of coordinates, essential for the proper localization of physical objects in space. Poincare (1923), in his classical analysis of the concept of space, recognized that we locate external objects in reference to our own body and that we apprehend spatial relations between objects only in relation to our own body. Interference with the establishment of this referential body axis results in selective impairment of motor behavior, as we have shown (Dubrovsky et al. 1974).

Concomitant with the electrophysiological study of the organization of telereceptive stimuli to motor cortex, we are analyzing the role of dorsal column afferents (a proprioceptive and somesthetic path) in a sequentially organized motor act (Dubrovsky et al. 1971, Dubrovsky and Garcia-Rill 1973). Cats are trained to jump up to release a piece of raw chicken liver attached to a vertically oriented, revolving wheel. The wheel is rotated by a motor of variable speed and testing is done with constant speed for all animals. The cats jump from a force transducer platform. Components of force are recorded in three axes on magnetic tape and converted for digital computer processing. The time of jumping in relation to the position of the rotating wheel is evaluated by attaching to the wheel a small magnet that activates a switch attached to the rotating axis. Each revolution is then marked by a pulse generated by the switch and recorded with the three components of force. The biomechanical investigation is complemented by high-speed cinematographic analysis of the movement.

Behaviorally different sequences of the act are independently analyzed by studying the following parameters: efficiency, accuracy, tracking, and searching index. Efficiency is evaluated as the percentage of successful releases of liver, without taking into account the precision of execution. Accuracy is expressed as the frequency with which an animal hits the holder instead of the target; i.e., an animal is less accurate the more it hits the holder. Tracking of the released liver in space is assessed in terms of the ability of the animal to localize it on the floor within 3 sec after it lands. Finally, the searching index is the frequency with which an animal attempts to localize a piece of liver after an unsuccessful attempt to release it.

After section of the dorsal column above the C1 level, significant impairment in all behavioral indices was observed. The following parameters, directly related to force, were also significantly decreased (Table 1): (1) height of jump,(2) time in the air, (3) maximum resolved force, and (4) peak to mean force ratio (an indication of the speed at which the cat developed the maximum muscular force).

Film analysis showed that intact cats consistently extended their limbs in a smooth and progressive way towards the liver in order to release it. The distance between the tips of forelimbs remained more or less constant during flight. Postoperatively, the extension of the limbs was interrupted by fast flexion movements and the distance between tips increased significantly during flight.

Impairment in force development after surgery may relate, in part, to sectioning fibers from skin mechanoreceptors conveying information on limb loading conditions. Marsden et al. (1972) showed the importance of cutaneous afferents for load compensation in proportion to force and suggested a transcortical mechanism for its development. Furthermore, we think that section of the dorsal column suppresses an important path for cutaneous afferents involved in supraspinal mechanisms of synchronization of muscle activity (Milner-Brown et al. 1975). These authors suggested that the mechanisms for exertion of large, brief forces (e.g., jumping) may result from strengthening reflex pathways involving a fast, lemniscal route to the cortex.

Before surgery, the animals jumped up with a consistent stereotypic pattern including the direction of takeoff. After dorsal column section, the initiation of jumping was delayed and more variable in relation to preoperative timing, and the cats showed a significant change in the direction of takeoff, suggesting a change in strategy of the animal while on the ground.

The postsurgical impairment in reaching the target may be associated with the fact that the dorsal columns are the exclusive afferent path to brain centers for muscle spindles and low threshold joint afferents from the forelimbs. Muscle spindles convey information on the length and speed of changes in length of muscles. Low threshold joint receptors yield information on joint position.

Since position sense is necessary for knowledge of both the spatial and temporal parameters of movement initiation, section of the dorsal columns may impair the ability of an animal to readily initiate the sequence by interrupting fibers carrying impulses from muscle spindles and low threshold joint afferents from the forelimbs. Both types of information are involved in kinesthesis. Absence of information from forelimb musculature on length, and changes in length, of the muscles can also seriously impair the accuracy of a motor sequence involving the use of these extremities. Decreased cutaneous signals should further reduce the accuracy of forelimb movement because skin sensation is essential for refined motor acts (Granit 1975).

Table 1. Effect of Dorsal Column Section on Mechanical Performance.[1]

Behavioral Index	Preoperative	Postoperative	Probability
Height of jump, meters			
$H=\frac{1}{2g}\frac{(I_z)^2}{m}$	0.3118	0.1469	$p<.001$
Time in the air, sec	0.6139	0.5613	$p<.02$
Work, joules			
$W=mgH$	9.721	4.582	$p<.001$
Maximum resolved force, Newtons			
$F=\sqrt{F_x^2+F_y^2+F_z^2}$	82.15	46.914	$p<.001$
Peak/mean force rate	2.417	1.500	$p<.002$

[1] Results from one cat representative of a group of three. H = height of jump; 1 = impulse at takeoff; g= acceleration of gravity, 9.81 meters/sec^2, x,y,z = axes of rectangular coordinate system (z vertical); m = mass of cat; W = work; F = force.

Tracking deficits, we believe, are due to the interruption of proprioceptive signals from the dorsal neck region ascending through the dorsal columns. Low threshold muscle afferents from deep and superficial dorsal neck muscles project to zones corresponding to the frontal eye fields of the cat brain (Dubrovsky 1974, Dubrovsky and Barbas 1975). These signals transmitted through the dorsal column may play an important role in proper coordination of eye-head-movements in complex motor acts requiring movement of the head relative to the entire body while the body is in motion. For instance, we recently found that afferents from extraocular muscles also project to frontal eye field areas in the feline (Dubrovsky and Barbas 1977).

The bizarre behavior of lesioned cats–frequently searching for a target that has not been released–may be a manifestation of the disruption in the organization of an integrated serial movement that occurs when essential information for programming of the act does not reach higher brain centers. The disturbances in timing of jump behavior after surgery may be partially related to proprioceptive deficits. "Time" appears to be a derived concept in the central nervous system (Piaget 1970). In light of current knowledge of muscle spindle physiology (Matthews 1972), we suggest that central processes for the construction of precise timing strategies in movements are based, at least in part, on information conveyed by the spindles to telencephalic areas. This would include information concerning changes in muscle length (distance traversed by the body) and the speed at which this change in position took place. Time can then be derived from this information.

Results of experiments reviewed here support the preponderant role played by movements of the body and extremities in the genesis of the concept of space, as originally proposed by Poincare (1923) and later developed and extended to the concept of time by Piaget (1970). With respect to the function of teleproprioceptive and cutaneous input in motor control, our investigations suggest that visual signals arriving at the motor cortex mainly in zones corresponding with axial and proximal body regions, are probably related to tracking functions, i.e., bringing the limbs to a target. Control of accuracy, precise timing, and force to be developed during movement appear to be related to information originating from proprioceptive and cutaneous receptors.

METHODOLOGICAL CRITERIA FOR THE VALIDATION OF MOVEMENT-RELATED POTENTIALS

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Several scalp-recorded macropotentials, of distinct functional origins, can become synchronized temporally with the occurrence of abrupt voluntary movements of the hands or fingers. These movement-related potentials (MRPs) also superimpose spatially across the Rolandic region even though most peak elsewhere. It is not surprising, then, that tight methodological control and extreme caution in measurement are essential to differentiate optimally this spatiotemporal mixture of MRPs into functionally distinct components. Moreover, most studies of MRP and CNV research are probably uninterpretable with regard to which component was manipulated and measured, simply because investigators have not used methodologies shown to be essential for effective differentiation of MRP components (Deecke et al. 1969, Gerbrandt et al. 1973, Deecke et al. 1976, Gerbrandt 1977). Thus, when investigators compare the effects of an independent variable on "the readiness potential," it is uncertain whether a readiness potential or a compound potential of several functional origins is being affected by the variable under study. In order to put known considerations about the possible sources of "conceptual confounding" into a useful perspective, this review will be used to derive a methodological checklist for evaluating MRP results.

Investigators usually assume that there is a unitary readiness potential (N1) that can be recorded in isolation, even though MRP research indicates that this negative sustained potential (cf. Fig. 1, top trace) is easily contaminated by other movement-adjacent activities (e.g., P1, N2, N3, P2, and artifacts). This review will describe procedures regarded to be essential in distinguishing N1 from these other activities. Because procedures that are helpful in isolating N1 from other components include methods for isolating these confounding activities, this review should also be useful to investigators interested in MRP components other than N1. The methodological considerations discussed here also apply to CNV research because voluntary movements are involved in most CNV paradigms. Evidence suggests, for instance, that the CNV is enhanced by requiring an overt motor response (Donchin et al. 1973, Irwin et al. 1966). Late stimulus (S1)-linked SPs are also confounded by superposition with response-linked negative SPs preceding movement (Rohrbaugh et al. 1976, Rohrbaugh et al., in press).

What factors, then, need to be considered to isolate N1, functionally, from confounding components such as the CNV and other MRPs?

Technical Factors

The history of MRP research began with failures by several investigators to observe any potentials preceding self-paced, voluntary movements (Bates 1951, Caspers et al. 1963, Low et al. 1966, Donchin and Lindsley 1967). The first two failures are attributable, in part, to the fact that an averaging computer was not used. Since these potentials average about 5 μV, while background EEG often varies between 10-50 μV (S.D. = 10 μV), a clear and reliable visual resolution (Signal-to-Noise Ratio = 4) requires at least 64 averaged trials.

$$\text{Number of trials} = \left[\frac{\text{S.N.R.} \times \text{S.D.}}{\text{N1 ampl.}}\right]^2$$

To obtain quantitative data, such as onset latencies and topographic voltage gradients, some investigators recommend using several hundred (Vaughan et al. 1968), or even a thousand trials (Deecke et al. 1976). Notice in Figs. 6 and 8 of Deecke et al. (1976), for example, that 0.5-1.0 μV of EEG noise still remains after averaging 630-1082 trials. The inescapable conclusion is that, in some subjects, a 10-μV noise estimate is far too conservative. Therefore, more than 64 trials need to be averaged to resolve, properly, many of the MRP components that may superpose upon N1 and contaminate its measurement and functional interpretation.

Inadequacies in averaging, however, cannot entirely explain these early failures, since premovement

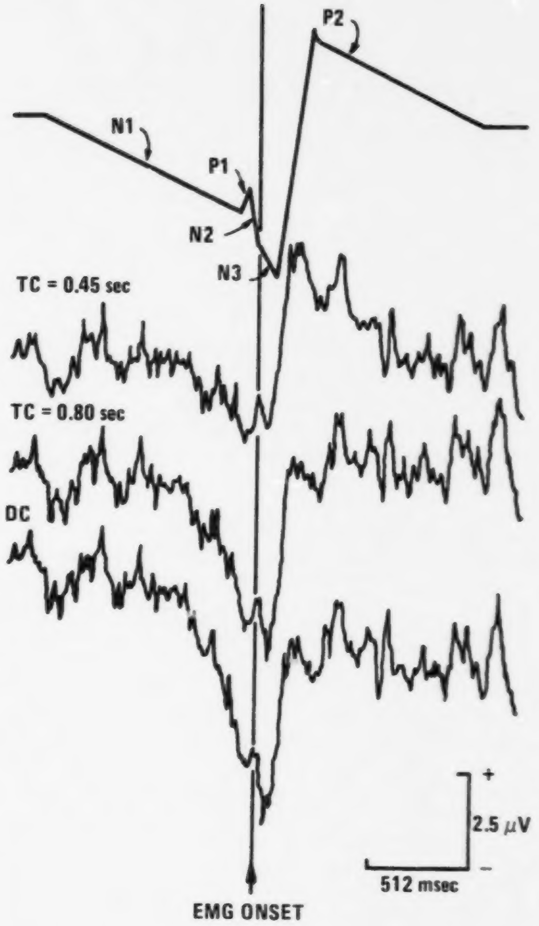

Fig. 1. Top trace: schematic of MRP waveform indicating temporal relationship of each component to EMG onset (vertical line), using abrupt hyperextension of the dominant index finger. Traces 2-4: actual MRPs of a single subject simultaneously recorded in three amplifiers with different time constants. Each trace is an average of 64 movements (dominant index finger hyperextension). Recording site located over presumed motor cortex (0% site), contralateral to movement, as shown in Fig. 3.

potentials such as N1 or P1 under some conditions can be visualized in single trials (Gerbrandt et al. 1973, cf. Fig. 3; Gerbrandt 1977, p182). Failures to observe N1 have also been reported when even smaller signals were apparent in averages (Low et al. 1966, Donchin and Lindsley 1967). The problem in the latter study may have been the time constant of the recording system. As Deecke et al. (1976) noted, if it is assumed that N1 onset averages about 0.8 sec before the start of EMG activity, N1 amplitudes will be reduced by about one third when a time constant of 1.2 sec is used:

True amplitude = Recorded amplitude x

$$\left[1+\frac{\text{N1 duration of 0.8 sec}}{2 \cdot \text{TC of 1.2 sec}}\right]$$

Fig. 1 (traces 2-4) compares N1 activities as a function of recording dc versus TCs of 0.80 and 0.45 sec. At least 22% and 67% of the N1 signal are lost, respectively, by using these shorter time constants. In this case, N1 onset (in dc recordings) occurred 550 msec before EMG onset so that the attenuation of N1 by shorter TCs was not as severe as it would have been with N1s of more typical durations. Nevertheless, with a TC of 0.45 sec, this short-duration N1 was reduced near the EEG noise level. Since the ratio of N1 to other components of shorter duration becomes smaller, it is more heavily contaminated by other components when short TCs are used.

Another problem that could develop when RC coupling is used is capacitative unloading of N1 before or during movement onset. Spuriously, "P1s" or "P2s" would then tend to correlate with N1 in amplitudes, topography, and latencies of onset. Variables that affect the slope of N1, such as duration of response (Deecke et al. 1976), may differentially change the temporal locus of this capacitative unloading.

Instructional Factors

In the study by Low et al. (1966), neither a lack of averaging nor a problem with time constants accounts for the failure to record N1 in advance of self-paced button-pressing. What appears to be an N1 potential was, however, recorded in an average of only 12 trials when subjects pressed a button to avoid a loud buzzer (Sidman avoidance tasks). Although this negative wave may be conceptualized as an "expectancy" of the buzzer, subjects were so successful in avoiding this stimulus that they should rarely have *expected* to hear it.

N1-like activities have also been recorded in numerous studies where button-pressing was not explicitly reinforced (e.g., McAdam and Seals 1969, Rohrbaugh et al. 1976, Otto et al. 1977). What is more likely, then, is that the Sidman avoidance schedule highly involved the subjects in button-pressing, that subsequent button-pressing alone constituted an extinction of this involvement, and that involvement in the action is essential for the appearance of N1. Without strong intentional participation (Kornhuber and Deecke 1965) or incentive-motivation for correct responding (McAdam and Seales 1969), N1 amplitude may decrease by more than half.

Criteria For N1 Validation

In experiments where N1 activities were reliably recorded (e.g., Vaughan et al. 1968, Deecke et al. 1969, Gerbrandt et al. 1973), even though reinforcements or instructional sets were not separately manipulated as experimental variables, subjects were explicitly instructed what to move, when to move, how rapidly, and how long to hold the movement. Baseline EMG activities were continuously sampled to ensure that subjects followed instructions. This type of instructional set may demand the involvement of subjects and thus enhance N1 because the response form is specified in advance by the voluntary plan of action, rather than by triggering nonspecific motivational processes (arousal). N1 onset is earlier and hemispheric asymmetry possibly greater when a longer duration response is required (Deecke and Kornhuber 1977). Papakostopoulos and Cooper (1976) have also shown that, during the preparatory interval before a response, the background reflex field is specifically repatterned to assist the impending voluntary movement. This reduction of stretch reflexes, which would otherwise antagonize the intended action, may play an important role in smoothing and accelerating action sequences.

It appears then, that N1 reflects a process functionally significant in readying the central and peripheral nervous systems according to the specific actions that are intended. Experimenters must ensure, therefore, that, during the period of preparation for responding, subjects attend only to the exact parameters of response; e.g., type and extent of movement, force, speed, duration and interval of primary response, and specific sets to eliminate adventitious responses. When a movement in MRP or CNV research is described simply as "button-pressing," too little attention is probably being paid to motor control by either the subject or experimenters to know whether or not N1 functions are being reliably engaged and sampled.

Spatiotemporal and Triggering Factors

Few MRP investigators have provided evidence that appropriate steps have been taken to minimize the spatiotemporal superposition of N1 and artifactual or other MRP components. A crucial consideration is whether the N1 distribution is distinct from the distributions of other components known to encroach on the spatial and temporal domain of N1. Since N1 seems to reflect an action-smoothing function via specific readiness processes antecedent to specific actions, N1 asymmetries are differentially focused over the pyramidal motor system contralateral to the moving hand in right-handed subjects (Vaughan et al. 1968, Deecke et al. 1969, Gerbrandt et al. 1973, Deecke et al. 1976).

This topographical feature is illustrated in Fig. 2, where the asymmetry of N1 is 35% less over presumed somatosensory cortex (-25% site) relative to motor cortex (0% site). Electrode locations are defined in Fig. 3. The attenuation of N1 asymmetries away from motor cortex occurs so rapidly that, in monopolar comparisons of MRPs contralateral and ipsilateral to movement, significant asymmetries are observed only over this pre-Rolandic site (Gerbrandt et al. 1973, Deecke et al. 1976). It is quite likely, then, that the C3 and C4 sites used by many MRP

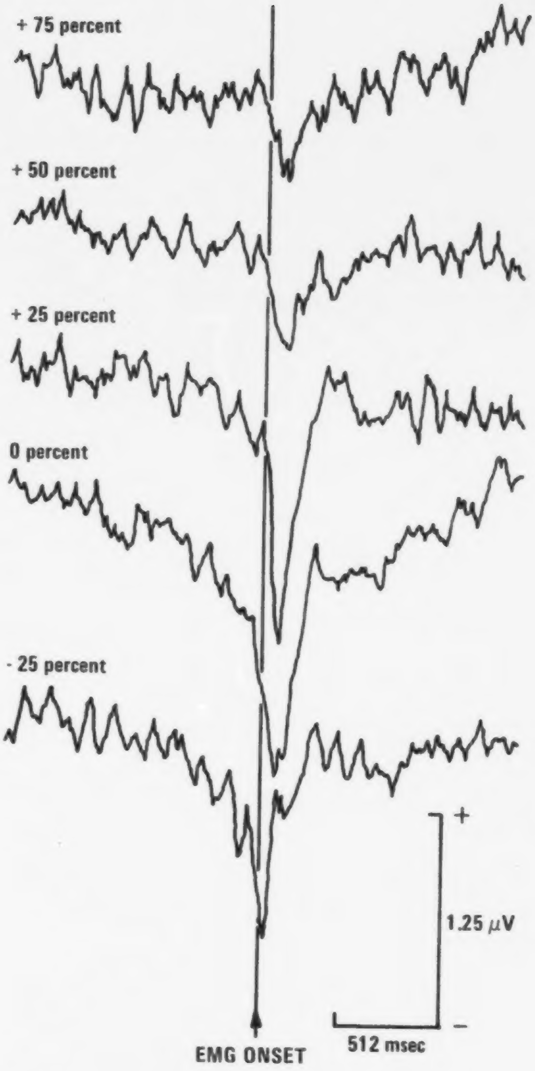

Fig. 2. Bipolar derivations (contralateral minus ipsilateral to dominant index finger hyperextension) are shown representing five paired recording sites. The waveforms at each recording location are grand averages (N = 352) over five subjects. The earliest average EMG onset is indicated by a vertical line. Recording sites shown in Fig. 3.

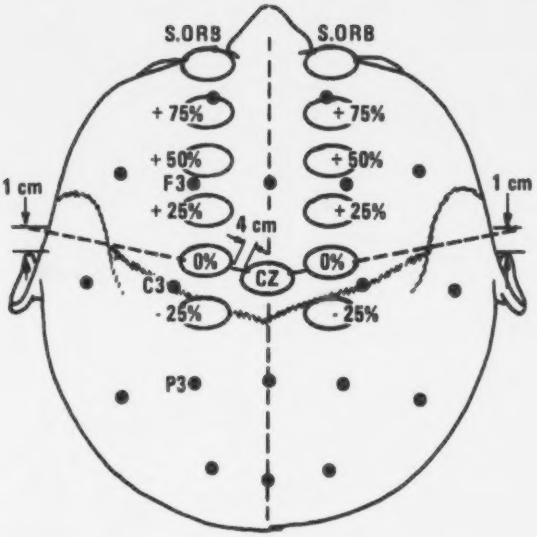

Fig. 3. The scalp-recording sites used for the data presented in Fig. 1, 2 and 4 are shown in relationship to the 10-20 system.

and CNV investigators are too far posterior for maximal sensitivity to N1 asymmetries since these sites are closer to the Rolandic line on the declining gradient of N1. At the same time, these more posterior locations maximize the chance of mixing attenuated N1 activities with activities of different functional origin, as discussed below. Depending upon the method used to locate the Rolandic line (Vaughan et al. 1968, Deecke et al. 1969, Gerbrandt et al. 1973), *the pre-Rolandic electrode should be situated 1-2 cm anterior to the C3/C4 position.*

Even when electrodes are placed optimally for sampling N1 asymmetries, it may be difficult to recognize them. Although the recording ipsilateral to movement was about 60% smaller than contralaterally in the study by Vaughan et al. (1968) and 30% smaller in the study by Gerbrandt et al. (1973), it was only about 10% smaller (and not statistically significant) in the work of Deecke et al. (1969) and 20% smaller in subsequent work (Deecke et al. 1976). Indeed, very large asymmetries may indicate the superposition of asymmetrical MRP activities with an origin other than N1. Deecke et al. (1976) showed that the ipsilateral N1 was 55% smaller than contralateral only when measured from baseline to the point of EMG onset. They note that the added asymmetry is largely due to contamination of the N1 measure by N2 activities that occur 20-100 msec before EMG onset and are more focused than N1 over the motor cortex contralateral to movement. They note further that, if one triggers MRP averages from mechanograms, photocells, or even skin-surface EMG electrodes (rather than the first intramuscular EMG activity of the principal effector), N2 activity is more likely to be confounded with the N1 measurement because (1) the earliest EMG activity is not detected and (2) there is greater temporal jitter between N2 and movement-estimated onsets compared to EMG onsets. If total EMG quiescence is not achieved prior to abrupt movement (documented by multiple-EMG recordings), and if the most sensitive EMG replacement is not used, then N2 activities could begin as soon as the subject begins to prepare (i.e., as early as 1.5 sec before the actual movement).

This criticism by Deecke et al. is so lethal that the validity of most MRP and CNV research is suspect. Perhaps no research group has succeeded in measuring N1 free from N2 contamination since it is unlikely that the same motor units sampled from a given electrode are always the first motor units to fire. Pilot work by the Kornhuber group shows, however, that the magnitude of this functional rotation among motor units and muscle groups is probably not greater than 100 msec (cf. Fig. 2B of Deecke et al. 1976), at least in the Ulm experiments where the movement is simple and abrupt and subjects are all highly practiced in silencing intramuscular motor activity across several muscle groups.

Given that the average N2 wave commences 54 msec before the average EMG onset, it may be assumed that N2 would not be appreciably confounded with N1 more than 154 msec (100 + 54 msec) before the average EMG onset. No other group has studied the topography of N1 while systematically triggering MRPs from the onset of intramuscular EMG activity, and no other group has estimated the onset latencies of N2 compared to EMG in a topographic study. Since only the Ulm group has determined how early N2 can occur prior to an intramuscular trigger, and since the extent of functional rotation has not been estimated, the extent of N2 contamination elsewhere is as yet unknown.

Vaughan et al. (1968) triggered averages from a skin-surface EMG location, a procedure which raises doubts about the sensitivity of detecting the earliest EMG onset. However, they used a simple, abrupt movement (hyperextension of fingers or hand) with a superficially located principal effector *(extensor digitorum communis).* Deecke et al. (1976) found that estimates of N2 onset latency and amplitude obtained from intramuscular EMG, skin-surface EMG, and mechanogram triggering were sufficiently similar with a simple, abrupt flexion of the index finger to conclude that N1 and N2 were not confounded in this case. Using a simple, abrupt hyperextension of the index finger, Gerbrandt (1977) also reported that intramuscular triggering from the *extensor digitorum communis* did not change the onset latencies of the

N3 component from earlier estimates obtained with a photocell trigger and skin-surface EMG electrode (Gerbrandt et al. 1973). If it can be assumed that the functional rotation among motor units is similar for a simple, abrupt hyperextension and flexion of the index finger, and that EMG silence and sensitivity to earliest onset were achieved, then the rotation-plus-N2 onset safety margin of 154 msec estimated by Deecke et al. (1976) can be used for measuring N1 in the studies of Vaughan et al. (1968) and Gerbrandt et al. (1973). Vaughan et al. did not terminate N1 measurement systematically at 154 msec or more before EMG onset. Contamination of N1 by N2, therefore, probably accounts for the large N1 asymmetries reported (62% smaller ipsilaterally). N1 measurements in the Gerbrandt et al. work are probably not contaminated by N2 since measurements were begun 150 msec before EMG onset and the earliest EMG onset was determined for each subject. Although we did not report onset latencies for the premovement N2, reanalysis of the data using bipolar derivations clearly shows an N2 component arising 46 msec before EMG onset (cf. Fig. 2, 0% site), whereas N1 onset occurs at an average of 794 msec before EMG onset.

Task Factors

Most other N1 experiments (and probably all CNV experiments involving a terminal motor response) are uninterpretable with regard to N1 contamination by EMG-adjacent activities. Complex flexion responses such as balloon-squeezing, telegraph-keying, button-pressing, or squeezing a hand dynamometer have typically been used. Even though some investigators attempted to sample EMG activities associated with the movement, an amazing number of principal effectors are involved in complex responses. Kinesiology tests offer little suggestion as to which effectors might have the earliest onset. Often, principal effectors are deep muscles that are inadequately sampled by skin-surface EMG electrodes. Arm and body positions required to maintain contact with the apparatus – "ready" to respond – make it difficult to achieve EMG quiescence. Some devices require the application of large forces (1-20 kg) that probably involve functional rotation across an extensive muscle field.

Subjects must also expect and encounter extrakinesic and tactile resistance against the apparatus, factors that undoubtedly introduce potentials that would not occur in simple unimpeded movement situations. The use of oscilloscopes or other on-line feedback signals may similarly introduce confounding nonmotoric expectancies. These problems were compounded in many studies by the use of short intermovement intervals (3-4 sec). It is difficult for both subjects and experimenters to ensure EMG quiescence and stability in such a short interval after movement. These kinesiological questions require extensive documentation to show that the earliest EMG activities have been sampled and that EMG quiescence has been achieved. Since N2 may be the scalp-recorded integral of specific commands or initiations of *every* muscle group cortically activated during movements, these methodological errors may introduce N2 confounding more than 150 msec prior to the arbitrarily determined EMG onset. The 150-msec estimate obtained in early work with simple, abrupt movements (Deecke et al. 1969, Gerbrandt et al. 1973) probably does not apply to these more complex movements.

Adventitious Movement Factors

Even when the methodologies seem adequate for attaining good estimates of EMG quiescence and earliest EMG onset for the responding limb, adventitious or occult events (not primarily involved in self-paced or planned movements) may occur that produce potentials that summate with N1. It is essential, therefore, to place electrodes over all recording locations where possible contaminating (superimposed) sources of activity appear differentially compared to N1. Otherwise, one cannot verify that the observed component is behaving as a function of N1 rather than extraneous factors. Routine placement of electrodes for detection of vertical eye movements (EOG), for example, is essential for ruling out this source of artifact (Hillyard and Galambos 1970). Requiring eye fixation on an external reference, denying subjects view of their own movements, and pretraining of subjects by having them watch their own eye movements reduce, but do not entirely eliminate, artifactual eye movements (Papakostopoulos et al. 1973). Routine monitoring of eye movements is essential (Wasman et al. 1970).

Although horizontal eye movements do not contribute *artifactually* to scalp recordings when a linked-earlobe reference is used, potentials preparatory to eye movements may appear over Rolandic and frontal regions even when averaged EOG recordings may not indicate artifactual contamination (Becker et al. 1972, Syndulko and Lindsley 1977, Rosen et al. this volume). These potentials may be functionally related to N1 in the sense of involving readiness processes, but not specifically associated with voluntary hand movement and may thus confound measurements of the symmetry and topography of components related to hand movement. Both horizontal and vertical eye movements should, therefore, be monitored at all times. Any trials showing orbital-related activities should be deleted before averaging.

Investigators should also demonstrate that other extracranial sources of N1 contamination (e.g., glossopharyngeal and neck EMG artifact) have been eliminated. The neutrality of the reference electrode

Table 1. Electrode Sites and Waveforms Needed to Distinguish N1 Spatiotemporally from other Components*

Active electrode sites	No.	Waveform derivations	No.	Purposes of derivations
External canthus	1	EC – LE	1	Monitor horizontal eye movements, differentiate eye movements from "asymmetrical and reversed N1"
Supra-orbital(C&I)	2	SO(C&I) – LE, SO(C) – SO(I)	3	Monitor vertical eye movements, confirm differential presence of "reversed and symmetrical N1," confirm narrowness of N1 distribution
+25%(C&I) or F(3&4)	2	+25%(C&I) – LE, +25%(C) – +25%(I) or or F(3&4) – LE, F3 – F4	3	Confirm presence of N3, confirm narrowness of N1 distribution and difference from N3 distribution, confirm narrowness and difference in N2 vs. N1 and N3 distributions
0%(C&I) or modified C(3&4)	2	0%(C&I) – LE, 0%(C) – 0%(I) or or MC(3&4) – LE, MC3 – MC4	3	Confirm focus of asymmetrical N1, confirm focus of N2
-25%(C&I&Z) or P(3&4)	3	-25%(C&I&Z) – LE, -25%(C) – -25%(I) or P(3&4&Z) – LE, P(C) – P4	4	Confirm focus of symmetrical P1, confirm posterior distribution of symmetrical N1, confirm posterior distribution of P2, confirm "reversed" N3 postcentrally

*Abbreviations: C = Contralateral; EC = External Canthus; F = Frontal; I = Ipsilateral; LE = Linked Ear Reference; MC = Motor Cortex; P = Parietal; SO = Supra-orbital; Z = Midline. Electrode sites are illustrated in Fig. 3.

should also be demonstrated with a noncephalic indifferent electrode.

Electrode Derivation Factors

When all these procedures are employed, the proof of their effectiveness still rests in the demonstration that N1 is spatiotemporally focused appropriately and is distinguishable from other MRP components (P1, N2, N3, and P2) capable of occupying the same domain. A list of electrode derivations considered necessary to analyze N1 is shown in Table 1. Note that bipolar derivations (contralateral - ipsilateral) are also essential in most subjects to isolate N2 from superposition with symmetrical P1 activities (Deecke et al. 1969, compare the 0% sites in Fig. 2 vs. Fig. 4). Bipolar derivations are also helpful in distinguishing N1 from N2 activities because N2 is more symmetrical and differs temporally in slope of amplitude (Fig. 2). Notice, in addition, that N1 has a different distribution with bipolar vs. monopolar derivations. With monopolar recordings (Fig. 4), N1 is largest postcentrally, whereas in bipolar derivations (Fig. 2) N1 is 35% larger (at 150 msec before EMG onset) over the motor cortex.

An even greater contrast between monopolar and bipolar distributions is obtained when the postcentral electrode is moved posteriorly over the P3/P4 sites (Deecke et al. 1976), where N1 shows no asymmetry at all. The bipolar distribution seems to correspond more closely to specific readiness processes preceding specific actions (i.e., it is asymmetrical and focused over the motor cortex). The fact that motivational variables may differentially affect symmetrical compared to asymmetrical N1 activities (McAdam and Seales 1969, Kutas and Donchin 1977) suggests that these are functionally different types of readiness that should be separately measured.

Finally investigators should score records blind with regard to electrode site, condition, and subject to avoid experimenter bias about the existence of a

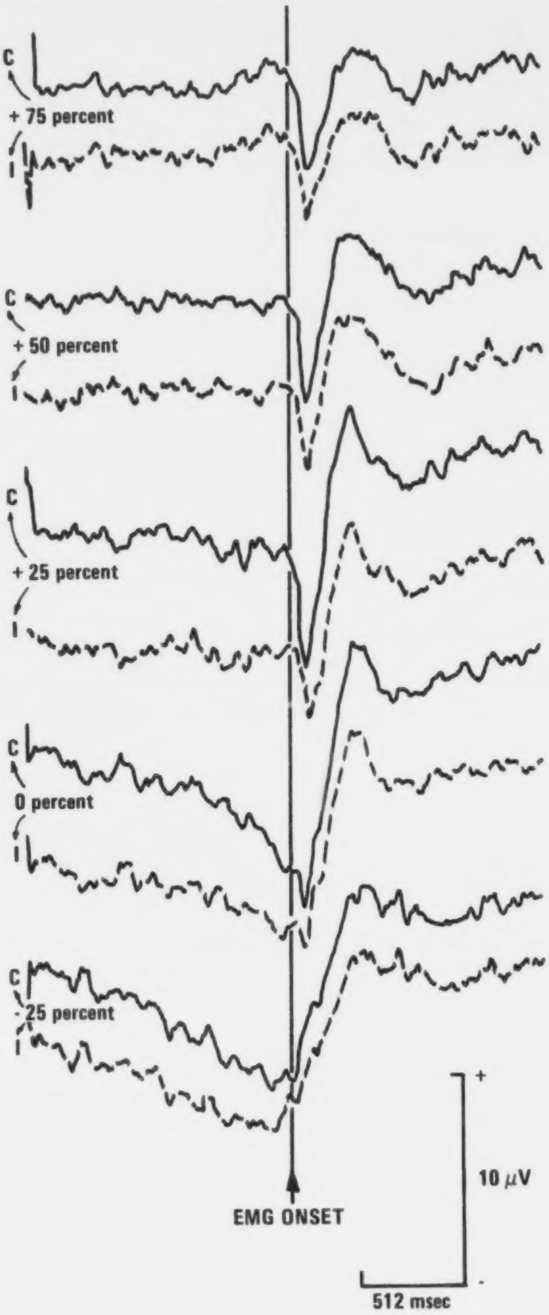

Fig. 4. Monopolarly-recorded MRPs (linked ear reference) for five pairs of electrodes (contralateral to dominant index finger movement = solid line; ipsilateral = broken line). Waveforms are grand averages (N = 352) over five subjects. Earliest average EMG onset indicated by vertical line. Recording sites located as shown in Fig. 3.

component. For instance, random fluctuations in EEG voltage may inadvertently be identified as N1 onset, or "P1" or "N2" bumps, even when such components may not be present (cf. possible "N2" at -25% site, Fig. 2). Peak-seeking algorithms which automatically select a maximum or minimum voltage point within a specified time window, for instance, will always provide an output value, regardless of the quality or nature of the input. Since all MRP analysis techniques are more or less susceptible to biases or limits of this type, investigators should explicitly state the set of measurement rules used (cf. Gerbrandt et al. 1973, Deecke et al. 1976).

Conclusions

The foregoing methodological considerations are summarized in Table 2 which is organized as a checklist for use in planning and evaluating MRP studies. The specific procedures listed in Table 2 can be reduced to three basic criteria for optimizing N1 resolution: (1) demonstrate clear visual resolution of N1 (signal-to-noise ratio = 4); (2) demonstrate clear spatiotemporal resolution of N1; and (3) demonstrate clear functional resolution of N1.

If previous MRP and CNV research is evaluated rigorously in accordance with this checklist, it may be concluded that N1 has rarely been recorded with sufficient methodological controls to ensure unconfounded measurement and interpretation. That is, in most studies the sustained negative potential associated with preparation for voluntary movement cannot be distinguished from other potentials of different functional origin. Indeed, so much data are brought into question that one must ask whether the criteria are too stringent and why so few investigators have applied them.

An analogy from the field of neuropharmacology may be helpful in answering these questions. A neurotransmitter is a chemical substance by which information is transferred from neuron to neuron. Three criteria must be met to conclude with certainty that a particular substance functions as a neurotransmitter (Julien 1978). These criteria are: (1) the compound must be contained in, and released from, specific presynaptic nerve endings; (2) control over the rate of release of the putative compound must mimic postsynaptic actions (excitation, inhibition) that follow from presynaptic nerve stimulation; and (3) there must be a mechanism of inactivation of the compound that shapes the time course of the "natural" transmitter action.

When students first hear how difficult these criteria are to satisfy in the central compared to the peripheral nervous system, they question whether it is "fair" to apply peripherally-devised criteria to the CNS. In the PNS or CNS, the purpose of the criteria

Table 2. Methodological Checklist of Procedures to Optimize Spatiotemporal and Functional Resolution of N1

1. *EEG Electrode and Recording Factors*
    - (a) Use appropriate electrode montages, including unipolar and bipolar derivations as shown in Table 1 and Fig. 3, to maximize spatiotemporal resolution.
    - (b) Use long time constants ($\geq$ 0.8 sec).
    - (c) Determine that reference electrode is neutral by use of noncephalic indifferent technique.
2. *EMG Electrode and Triggering Factors*
    - (a) Use appropriate recording methods, preferably needle electrodes inserted in principal effector muscles, to trigger averages from the earliest motor unit discharge.
    - (b) Determine degree of functional rotation among relevant motor units.
    - (c) Achieve stable periods of EMG silence ($\geq$ 4 sec) between successive movements.
3. *Task and Instructional Factors*
    - (a) Use a simple, abrupt, unimpeded movement that requires minimal support.
    - (b) Use long intermovement intervals ($\geq$ 10 sec).
    - (c) Use right-handed and left-handed responses (in right-handed subjects) to show lateralized N1 focus.
    - (d) Carefully instruct subjects to focus attention on relevant parameters of the required response and to inhibit all other movement. Monitor EMG to ensure compliance.
4. *Signal Averaging Factors*
    - (a) Average 64-1082 trials as necessary to achieve an EEG signal-to-noise ratio = 4
    - (b) Reject high-noise trials and high-noise subjects.
    - (c) Demonstrate that waveforms are not confounded by artifactual or adventitious potentials that are not primarily involved in the sel[illegible] movement (e.g., vertical or horizontal eye movements, glossopharyngeal or neck EMG activity, nonm[illegible]pectancies).
5. *Measurement Factors*
    - (a) Explicitly state the set of measurement rules used in data analysis.
    - (b) Measure each MRP component at the electrode location and with the particular derivation that maximally differentiates the component from other components (cf. Table 1 for N1).
    - (c) Determine the onset latency of N2. Measure N1 from the N2-free terminal point ($\geq$ longest rotational-plus-N2 onset point).
    - (d) Score records "blind" to electrode site, condition, and subject to avoid experimenter bias.

is to ensure that the compound in question, *rather than another,* is the one that is involved in transneuronal information transfer, *rather than some other function.* Application of these criteria in the CNS is very difficult, but positive identification of a neurotransmitter can only be claimed when these criteria have been met.

This checklist, like the neurotransmitter criteria, is meant to ensure that a particular functional component (N1) has been demonstrated in isolation. Shortcuts in applying N1 criteria simply may lead to uncertainty about what is being demonstrated. Hopefully, this review provides a systematic framework for evaluating past N1 research and will encourage a broader application and further refinement of criteria for demonstrating N1 and other component functions in subsequent MRP studies.

EFFECTS OF MOVEMENT ON SENSORY INPUT

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Sensory input is generally diminished when movement coincides with sensory stimulation if the two events are not related. This effect can be demonstrated by the study of evoked potentials in animal and man. Evidence related to the effects of movement on auditory and somatosensory evoked potentials is reviewed here. Visual evoked potentials are not considered because visual inputs are modified by ocular movements and pupillary contraction.

Animal Studies

Starr (1964) studied the influence of motor activity on click-evoked responses in the auditory pathway of the awake cat. Responses recorded from the round window, cochlear nucleus, inferior colliculus, medial geniculate body, and auditory cortex were of smaller amplitude when animals were moving. The extent of attenuation was roughly related to the extent of movement. When tendons of the middle ear muscles were sectioned bilaterally, responses recorded from subcortical stations did not decrease during movement, whereas cortical responses were still attenuated. Amplitude of cortical responses to an electric shock, applied through bipolar electrodes located along subcortical stations of the auditory pathways, decreased during motor activity if the stimulation was subthalamic, while it was unmodified by medial geniculate stimulation. This finding suggests that mechanisms modifying cortical responses do not influence the cortex directly, but act at intermediate sites.

Ghez and Lenzi (1971) studied changes in the transmission of somatosensory volleys to the medial lemniscus during a conditioned voluntary movement. Cats were trained to lift the right paw, press a lever at the onset of a tone, and then replace the paw on the ground. The right superficial radial nerve was stimulated, and responses were recorded in the medial lemniscus. Responses to stimuli were significantly smaller during active movement, with depression occurring between 100 and 200 msec prior to the lifting movement. Responses returned to control levels within 100 to 200 msec after the cat replaced its paw on the ground. During the period of postural fixation, responses did not differ from control values.

Ghez and Pisa (1972) attempted to identify the parameters of movement related to the change in lemniscal transmission. They found a negative linear correlation between the amplitude of lemniscal response and the logarithm of the velocity of the bar, determined at the instant the stimulus was delivered. Neither force exerted nor passive movement of the upper extremity produced noticeable changes. Ghez and Pisa attributed the attenuation of lemniscal potentials to central influences impinging on the cuneate nucleus.

Coulter (1974) showed that responses evoked in the medial lemniscus by stimulation of the contralateral forelimb in the awake cat were reduced in amplitude during gross motor activity. During discrete movements, depression of the lemniscal potential could be clearly related to the occurrence and duration of bursts of muscle activity. This depression was observed about 100 msec prior to EMG activity. Neither movement of the forelimb opposite to stimulation nor passive movements resulted in depression of the lemniscal potential.

Human studies

Broughton et al. (1964) noted a decrease in somatosensory evoked potentials (SEPs) during fist clenching. Giblin (1964) also observed a decrease when fingers were moved either actively or passively. Coquery (1971) and Coquery et al. (1972) showed that SEPs elicited by electrical stimulation of a finger increased during the 200 msec before the beginning of EMG activity and decreased during contraction when flexion was performed by the stimulated hand. SEPs increased when flexion was performed by the nonstimulated hand, but decreased during active and passive plantar flexion of both feet. Coquery concluded that both facilitatory and inhibitory influences act on the somatosensory pathway and that at least part of the inhibitory influence has peripheral origin.

Lee and White (1974) studied the effect of repetitive flexion and extension of the fingers on SEPs elicited by stimulation of the fingers. The most obvious change during movements of the stimulated hand was an increase in amplitude and a slight increase in latency of a late negative component. The enhancement of evoked potentials was specific to movements occurring in the immediate vicinity of stimulation, but was not limited to the contralateral area. Enhancement was maximal at the vertex and almost as prominent over the ipsilateral as the contralateral hemisphere. Lee and White suggest that the change in evoked potentials reflects an interaction between central efferent and afferent systems, a cumulative effect that probably occurs at several levels.

Papakostopoulos et al. (1975) compared cortical potentials following passive or externally paced displacement (EPD) to those related to similar but self-paced voluntary displacement (SPD) of the index finger. Secondly, evoked responses to brief electrical stimuli applied to the medial nerve at the wrist during SPD were compared with similar responses elicited in subjects at rest. After EPD, a clear evoked response could be seen from prefrontal, precentral, and postcentral areas, whereas, after SPD, only a diminished response could be seen in the precentral area. In the same way, electrical stimulation of the median nerve evoked clear responses in precentral and postcentral cortex when the limb was at rest. When stimuli were timed to occur during self-paced displacement of the index finger, responses were diminished in the postcentral area, but remained relatively unaffected in the precentral area. The evoked potentials returned to resting values 700 msec after the movement onset, even if the displacement was sustained. Papakostopoulos et al. interpreted the results as a movement-related gating action that selectively affects sensory input to somatosensory and motor cortex, the latter being less inhibited.

Hazemann et al. (1975) investigated the temporal relationship between self-paced movement and presentation of test stimuli. Evoked potentials were averaged in 10 successive epochs, extending from 880 msec before to 2.5 sec after movement. Auditory evoked potentials were attenuated in all epochs, with the greatest decrease appearing in the epoch just following movement. Somatosensory evoked potentials were similarly attenuated when movements were performed by the hand contralateral to stimulation. In the ipsilateral case, SEP amplitude was attenuated only when stimulation was administered close to the active muscle. It appears from these results that movement induces a generalized central modulation of sensory evoked potentials that reflect the degree of occupation of a single limited-capacity channel (Broadbent 1971). The same channel appears to be used selectively for the transmission of either afferent input or efferent output signals.

Summary

The amplitude of somatosensory evoked potentials has almost always been found to diminish when the stimulated part of the limb was moved. Generally, the decrease commenced prior to movement onset. The effects of contralateral and passive movements are not as clear. When studied, the auditory evoked potentials have also been found to diminish during movement in both cat and man. Explanations vary, but most authors suggest that mechanisms of interaction between voluntary motor activity and sensory input may operate at different levels of the central nervous system.

INFLUENCE OF FORCE, SPEED AND DURATION OF ISOMETRIC CONTRACTION UPON SLOW CORTICAL POTENTIALS IN MAN

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The first studies on the human cortical motor potential described the type of movement performed, but did not take into account the fact that movements may vary during the experiment. Since that time, studies have been completed that consider the physical parameters of movement, although these investigations generally examined only one parameter: force (Ford et al. 1972, Wilke and Lansing 1973, Kutas and Donchin 1977) or speed (Becker et al. 1976). Their results are difficult to compare since, for example, the movements are performed by segments of different limbs.

The present investigation seeks to examine the systematic influence of force, speed of force variation, and duration of maintained force on the cortical motor potentials associated with isometric contractions of the index finger while a subject regulates his performance through visual control of the mechanogram.

Methods

Thirteen subjects (8 male, 5 female, 20-40 years old) participated in this study. Subjects were comfortably seated in an armchair with forearm support and index finger immobilized at the last phalango-phalangian joint by a large plastic ring, rigidly fixed to a strain gauge. The subject was told to make an index dorsiflexion against this gauge. The apparatus allowed contraction to occur under practically isometric conditions.

In the three situations defined below, the subject controlled the mechanograms of his contractions on an oscilloscope screen 1 meter in front of him. Contractions, timed by the appearance of the oscilloscope spot, were performed every 4 or 6 sec by the dominant hand and were repeated 300 times for each condition. In the "force" situation, contractions performed with a great force (GF) (about 500 g) were compared to contractions of small force (SF) (about 200 g), achieved in the same time. In the "speed" situation (speed of force variation dF/dt), high-speed contractions (HS), done with 500-g force and achieved in about 160 msec, were compared to low-speed contractions (LS) in which the same force was achieved in 660 msec. For the "time maintained" situation, contractions involving 200-g force, achieved in 160 msec, were sustained for 500 msec (BS) or 1000 msec (CS).

A separate recording session was held for each situation. Ten subjects participated in the force and speed situations, and six in the sustained contraction situation. EEG was recorded from the rolandic area (C3 or C4) contralateral to movement, with a scalp electrode referenced to linked ears (Al, A2). The time constant was 0.7 sec. EMG was recorded by means of surface electrodes over the *extensor digitorum communis* muscle. EEG, EMG and mechanograms were recorded simultaneously on paper and magnetic tape. The averaged motor potentials of 300 successive movements were obtained from a CAT 400 with an analysis time of 4 sec. The averager was triggered from the mechanogram, with a Schmitt trigger used to obtain a stable threshold. The lag between reading and recording heads of the magnetic recorder allowed a 1760-msec delay of the EEG. Motor potentials were displayed on an XY plotter. For each condition, mechanograms were averaged in groups of 100 and 300 to ensure that instructions were observed.

Two subjects participated in supplementary recordings during which ocular and visual phenomena were studied. Contractions were performed under HS and LS conditions with and without visual feedback from the mechanogram on the oscilloscope in order to check for ocular tracking movements and visual afferents. Contractions were averaged, with all trials preceding, following, or simultaneous with ocular movement or blinking eliminated, as a test for electrooculogram diffusion. For these experiments, EEG was recorded from the contralateral Rolandic (C3 or C4), frontal (F1 or F2), coronal (F3 or F4), and occipital (O1 or O2) areas, and EOG was recorded with silver electrodes from the superciliary arch and the lower rim of the orbit.

The cortical motor potential was analysed in terms of component latency and amplitude. Latencies were measured from the beginning of the mechanogram to inflexion of the baseline for N1 and peak latency for all the other components. Amplitudes were measured from the baseline, 200 msec before the mechanogram for N1, at peak for N2, P2, and P′2. For P1 and P′1, amplitudes were measured from the preceding peak. Latency and amplitude values for each condition were compared for individual subjects and for the entire subject population. Mean values and standard deviations were compared by student's test for group data.

Results

Analysis of group data showed that force exerted (determined by the amplitude of the mechanogram) was 495 ± 147 g for the GF condition and 222 ± 41 g for SF. Speed of force variation (measured as rise time of the mechanogram) was 192 ± 46 msec in the HS condition, 851 ± 106 msec for LS, 200 ± 47 msec for BS, and 276 ± 58 msec for CS. For conditions BS and CS, maintenance time (defined as the duration of the plateau) was 506 ± 122 msec and 956 ± 211 msec, respectively. Therefore, subjects were able to follow instructions for force and duration maintenance, but speed of rise time seemed difficult to control. In every situation, speed of force achievement was slower than requested. There was an evident prolongation of rise time when movements were performed at slow speed or with sustained movement.

With visual analysis of motor potentials, positive components were characterized that differed from those classically described (Fig. 1). The classical motor potential (using the nomenclature of Gilden et al. 1966) has a premotor negativity N1, an inconsistent premotor positivity P1, a negativity N2 culminating after movement, followed by a positivity P2. As P1 precedes an increase in the slope of negativity (N1), the slope inflection was considered to correspond to P1 even when a distinct P1 was missing. A second minor positivity P′1 was noted after movement and preceding or following the N2 peak. P2 was usually followed by another positivity P′2 and, although P2 was at times a mere notch within P′2, usually two individual peaks were noted, either of which might be greater. A double-peaked configuration of late positivity is also mentioned by Arezzo and Vaughan (1975).

Amplitudes and latencies of components were measured for the six experimental conditions (Fig. 2). Mean values and standard deviations for the latencies are given in Table 1.

N1 latency ranged from -1600 msec to -320 msec, with an average of -980 msec. N1 was seen in all subjects for conditions HS, BS and CS, in 8 out of 10 subjects for condition GF, and in only 5 subjects for condition SF. Its amplitude did not vary significantly from one condition to another; however, its latency was significantly longer for sustained contractions (<.02) and contractions done with little force (<.02).

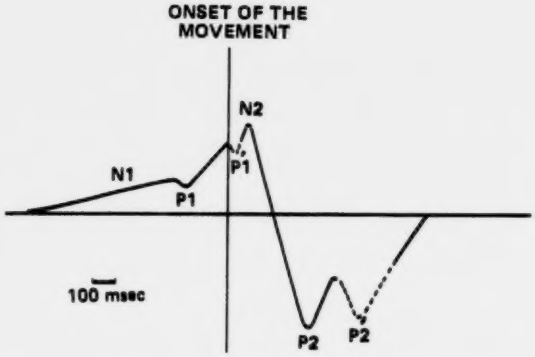

Fig. 1. Averaged cortical motor potential. Continuous line: components described by Gilden et al. (1966); dotted line: supplementary components described in this study.

Latency of P1 was from -440 msec to -20 msec, with an average of -204 msec. P1 was seen in only half the subjects for conditions GF, SF, HS, and LS while it appeared reliably and significantly earlier (<.001) for conditions BS and CS.

P′1 latency averaged 85 msec and ranged from 0 to 180 msec. P′1 was absent in LS, but appeared fairly consistently in all other conditions. Amplitude and latency were not systematically altered by other manipulations.

N2 latency was from -100 to +320 msec, with an average of +100 msec. N2 was consistently found for conditions HS, BS, and CS and was seen nine times for condition LS, eight times for GF, and seven times for SF. Its average latency was significantly longer (<.05) for condition LS compared to HS. N2 amplitude was significantly smaller (<.05) for condition SF compared to GF. For all other conditions, there was no significant difference in latency or amplitude.

P2 latency ranged from 220 to 500 msec, with an average of 367 msec. P2 was constant for conditions GF, SF, and HS, but was missing twice for condition LS and once for conditions BS and CS. Amplitude for the three latter conditions was significantly lower (<.001) than for other conditions.

P′2 was observed in nearly all recordings, but was missing in one subject for conditions SF and LS. P′2 amplitude was significantly higher (<.01) for condition HS compared to LS and for situation HS (<.05) compared to GF and SF. Latency was linearly correlated (0.92) with the duration of the mechanogram.

Because of the precocity of P1 in the sustained situation, the length of time between peak P1 and

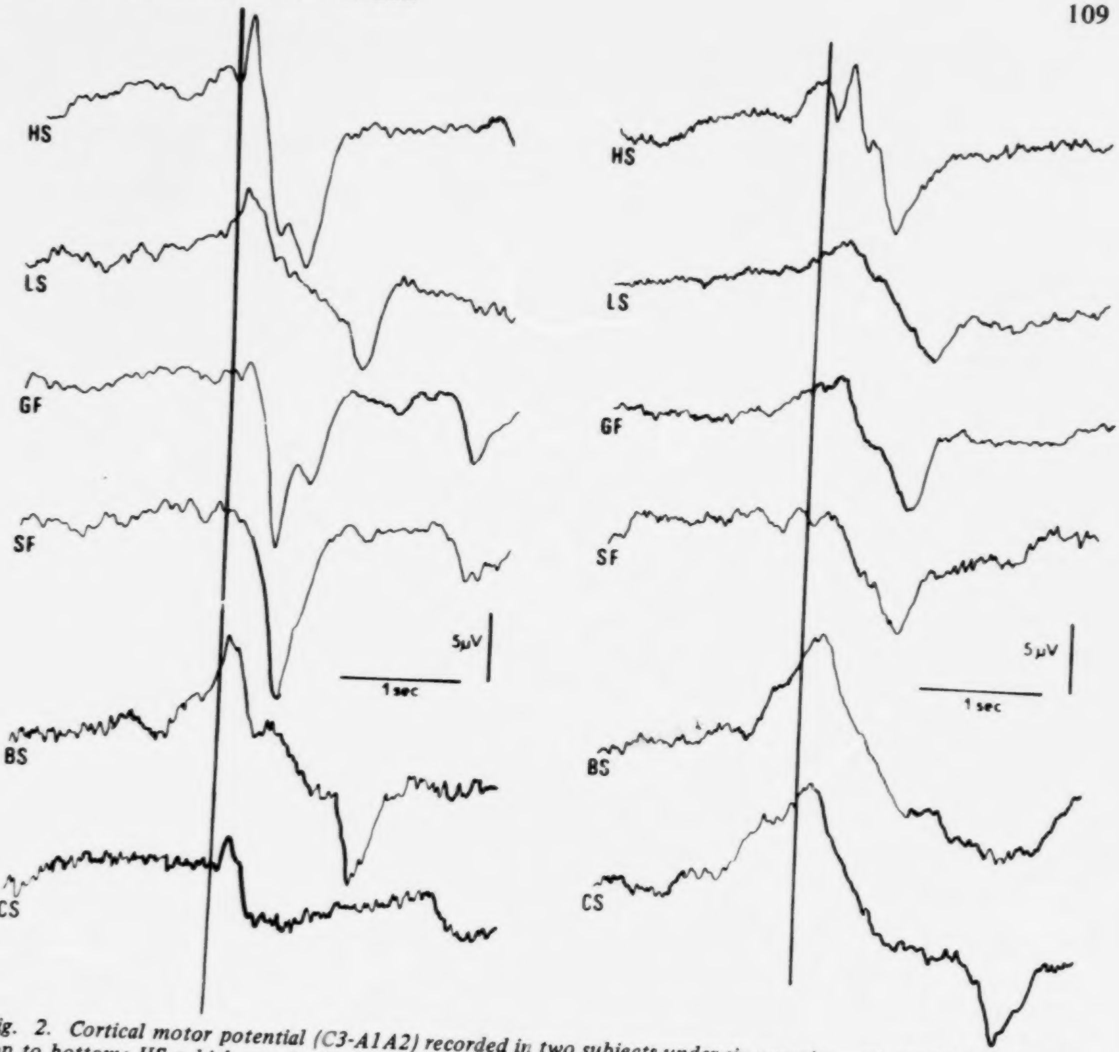

Fig. 2. Cortical motor potential (C3-A1A2) recorded in two subjects under six experimental conditions. From top to bottom: HS = high speed, LS = low speed, GF = great force, SF = small force, BS = briefly sustained, and CS = considerably sustained.

peak N2 was significantly longer (<.01) in the sustained situation compared to all other situations.

No significant difference in slow cortical potentials recorded from the rolandic area (Fig. 3A), or in EEG recordings averaged without ocular artifacts (Fig. 3B) was apparent whether or not visual control of the mechanogram was provided. These two tests excluded any contamination of the motor potential by extracerebral phenomena or by visual evoked potentials.

Discussion

Most authors who have studied the cortical slow phenomena associated with movement in man report high interindividual variability, whereas intraindividual phenomena for one kind of motor movement appear stable (Gilden et al. 1966; Deecke et al. 1969, 1973; Gerbrandt et al. 1973). The present findings and high standard deviations support these observations. Only Castaigne et al. (1969) report high intraindividual variability.

Modifications of slow potentials in relation to the force of movement have been studied previously by Ford et al. (1972), Wilke and Lansing (1973), and Kutas and Donchin (1977). In these three investigations, the amplitude of the motor potential increased with force exerted, thus affecting either the amplitude of the readiness potential (Ford et al., Donchin and Kutas) or negative-positive postmotor deflection (Wilke and Lansing). Furthermore, Wilke and Lansing observed the maximum negativity point at a constant latency from the beginning of EMG activity for a given subject and suggested that this measure might contain

Table 1. Means (m), Standard Deviation (σ), and Number (n) of Observations for the Latencies (msec) of Cortical Motor Potential Components as a Function of Physical Parameters of Concentration

		Force		Speed		Duration	
		500 g	200 g	160 msec	660 msec	500 msec	1000 msec
N1	m	-858	-1016	-855	-830	-1080	-1156
	σ	488	454	423	298	511	266
	n	8	5	10	8	6	6
P1	m	-120	-137	-224	-110	-326	-288
	σ	87	87	144	48	148	79
	n	5	5	5	5	6	5
P'1	m	110	104	77		70	64
	σ	47	50	72		47	51
	n	8	9	8		4	5
N2	m	80	57	98	194	106	108
	σ	97	90	97	117	65	48
	n	8	7	10	9	6	6
P2	m	370	376	348	407	336	356
	σ	62	62	34	98	55	88
	n	10	10	10	8	5	5
P'2	m	662	637	594	1104	1203	1745
	σ	133	107	81	266	268	296
	n	10	9	10	9	6	6

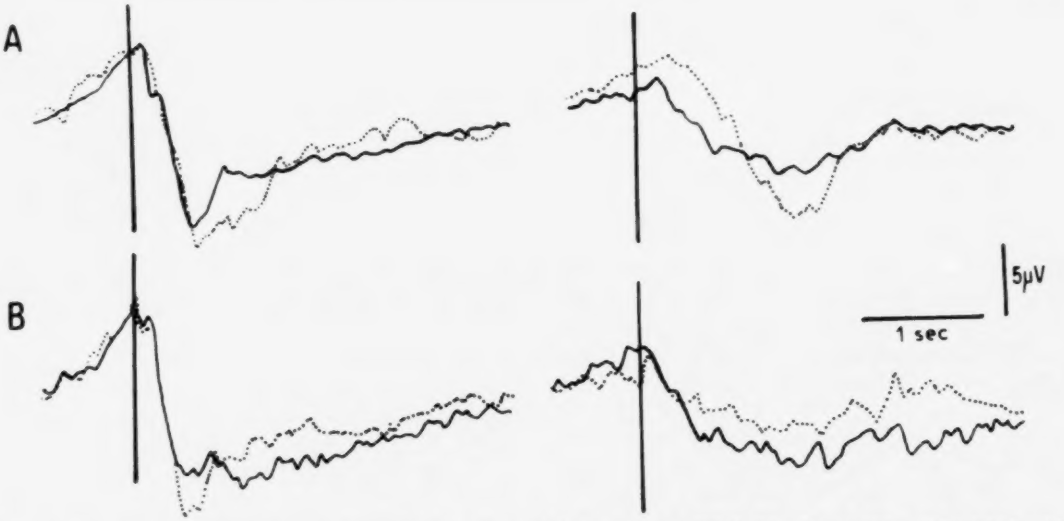

Fig. 3. A: Averaged cortical motor potential (C3-A1A2) for condition HS (left) and condition LS (right), with (dotted line) and without (continuous line) visual control. B: Averaged cortical motor potential (C3-A1A2) for condition HS (left) and condition LS (right), from the raw EEG recording (dotted line) and EEG recording without blinking and ocular movement (continuous line).

information about the force exerted during a movement. The only significant differences between GF and SF noted in the present work concern the amplitude of N2 ($p<.05$).

The influence of movement speed on motor potentials has been studied by Becker et al. (1976). Slow potential modifications affected N1; the latency was 800 msec for rapid and 1300 msec for slow movements and the amplitude was greater for slow movements. In the present study, no significant difference in latency or in amplitude was found, although HS and LS results tended to corroborate the preceding authors. The significant N2 latency changes were not described by previous researchers. The absence of P1 in low-speed movements, although difficult to interpret, is perhaps evidence in agreement with the conclusion of Becker et al. that the organization of slow movements is different from that of rapid movements.

Gilden et al. (1966) mentioned the influence of movement duration on the motor potential. They observed a positive wave beginning 50 to 150 msec after the start of EMG; the wave persisted, or diminished slowly, with sustained contraction. The behavior of this positive wave is similar to the wave P′2 described herein. Otto et al, (1977 and this section) have noted a prolonged positive variation during sustained motor response. Arezzo and Vaughan (1975) described a positive component, P3, at 265 msec, which might encode information on body position.

There appear to be no major contradictions between the results of this study and those of authors cited. Supplementary data, however, have been presented, allowing the definition of hypotheses and lending support to the hypotheses of others. The most important data concern the mobility of P1 latency, the relative stability of N1-P1 duration, the modifications of P1-N2 duration, and P′2 latency variations.

Apparently, the limits of variation in the motor potential are influenced by physical characteristics of contraction and depend upon the interrelations of its various components. The stable N1-P1 suggests that a general preparation mechanism is necessary for the performance of any contraction. The latency of P1 seems to be related to the type of motor contraction. Gerbrandt et al. (1973) hypothesized that P1 alone might be of motor origin. Deecke et al. (1973) proposed that it might be an electrophysiological expression of movement initiation by parietal and, perhaps, other association areas. Groll-Knapp et al. (1977) attributed P1 to processes of thalamocortical control of the efferent message.

The results tend to relate P1-N2 to the initiation and contraction control period. In the case of force control, the period is short but lasts longer when control affects speed (particularly the low-speed situation) or both speed of movement initiation and anticipation of its sustained nature.

Despite the difficulty of relating an animal model to the present research on humans, animal experimentation shows variations in cell activity according to force, speed of force variation (dF/dt), and sustained movement. Evarts (1968, 1969), using the monkey, demonstrated a relationship between the activity of certain cells in the pyramidal tract and the magnitude and rate of change in force, as well as the direction of displacement. Working with the same species, Smith et al. (1975) differentiated three cell types in the precentral cortex during performance of a sustained grip between the thumb and forefinger. Some cells behaved in a dynamic manner (increase or decrease in the frequency of action potentials related to movement). Their participation preceded movement by 500 to 750 msec; their activity rate could be related to the speed of force variation and, less frequently, to force alone. Other cells were static and came into play 0 to 400 msec after the beginning of movement; their activity vaguely increased with force and remained constant until the end of movement. Finally, a greater number of cells were of a mixed type, dynamic and static at the same time.

The stable temporal link between mechanogram commencement and P2 peak suggests that this wave is independent of contraction programming and variables of performance. This wave may represent the late component of the somatosensory evoked response, or the homolog of Sutton's uncertainty wave, as suggested by Gerbrandt (1977). In contrast, P2, which occurs at the end of movement regardless of its physical characteristics, varies in latency and becomes larger with brief contraction. Central and peripheral feedback mechanisms have often been proposed to explain electrical phenomena coming after movement onset. Papakostopoulos et al. (1974a), studying cortical potentials related to passive movements, attributed P2 to articular afferences. Megirian et al. (1974) observed an amplitude increase in rat motor potentials after novocainization of the moving paw and deduced that motor behavior is controlled by peripheral and central sensory feedback mechanisms. The hypothesis of a purely peripheral origin seems further weakened by the findings of Vaughan et al. (1970) that the overall configuration of the motor potential in the monkey is unchanged after deafferentation of the moving limb.[1]

In conclusion, the physical characteristics of contraction induce changes in P1 latency in response to temporal program complexity. P′1 is absent and N2 latency increases during low speed contractions. Lastly, P2 latency changes in relation to contraction duration.

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[1] Note Deecke's counterargument elsewhere in this section.

NEUROANATOMICAL ORGANIZATION OF THE PRIMATE MOTOR SYSTEM: AFFERENT AND EFFERENT CONNECTIONS OF THE VENTRAL THALAMIC NUCLEI.

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The *ventralis anterior* (VA) and *ventralis lateralis* (VL) nuclei comprise a major territory of the mammalian ventral thalamus, extending forward from the ventroposterolateral nucleus (VPL) to the rostral pole of the thalamus. Although the ventral tier nuclei of the primate thalamus have been carefully parcellated into cytoarchitecturally distinct subregions (Olszewski 1952), some boundaries, particularly that between the VL and the rostral region of the VPL, remain difficult to define.

It has been demonstrated anatomically and physiologically that the VA and VL nuclei form an important subcortical region of convergence for a number of structures related to the motor system. Afferent fibers to the VA-VL arise from the deep cerebellar nuclei (Angaut 1970, Mehler 1971, Kievet and Kuypers 1975, Rinvik and Grafova 1974, Chan-Palay 1977, Kalil 1977), from the *globus pallidus* (Kuo and Carpenter 1973), and *substantia nigra* (Carpenter et al. 1976). Intracellular recordings show that a single VL neuron can be influenced by synaptic inputs from several of these afferent fiber systems (Purpura et al. 1966, Sakata et al. 1966), and there is also considerable physiological evidence that VA and VL exert a strong monosynaptic influence on those neurons of the motor cortex that give rise to the pyramidal tract. Amassian and Weiner (1966) reported that pyramidal tract neurons could be monosynaptically excited by inputs from both VA and VL (see also Yoshida et al. 1966). Furthermore, by combining antidromic activation of VL neurons with stimulation of the cerebellum, Sakata et al. (1966) were able to demonstrate that fibers arising from the deep cerebellar nuclei synapse directly with VL neurons that, in turn, project to the motor cortex.

Despite the fact that the VL nucleus has long been recognized as the principal source of thalamic afferents to the primate motor cortex (Walker 1934, 1944), little is known about either the precise topography of thalamocortical connections arising from the ventral lateral nucleus or their distribution within cortical laminae. Still less is known about the cortical projections of VA. While it has been suggested that VA projects to area 6 (the premotor cortex) (Mettler 1947), large numbers of VA neurons survive hemidecortication (Powell 1952), which was thought to imply that VA sends relatively few axons directly to the cortex (see review by Carpenter 1967).

The strong influence of VA and VL on pyramidal tract neurons points to the importance of these thalamocortical pathways for the initiation and control of movement (Evarts and Thach 1969). Thus, it is surprising that so little is known about the detailed anatomy of these pathways. One of the major reasons for the paucity of studies on thalamocortical connections of the monkey VA and VL nuclei is the fact that, until recently, appropriate neuroanatomical methods for such studies were lacking. Almost all of our knowledge of the cortical connections of the VA and VL is derived from retrograde cell degeneration studies (Walker 1934, Chow and Pribram 1956), but these studies give little detailed information about the topography of this thalamocortical system. More recent studies (Kievet and Kuypers 1975, Strick 1976b) employed the horseradish peroxidase method and reported retrograde transport of the enzyme to the VA, VL, and rostral VPL after injections into the motor cortex of the rhesus monkey. Though a more precise topography can be obtained with this method, it cannot elucidate the laminar organization of thalamocortical fibers within the cortex.

Similar problems of methodology have also beset the detailed study of afferent input to the VA and VL nuclei, and thus little is known about the precise organization of cerebellar inputs to the thalamus. Fortunately, however, the autoradiographic method for tracing neuronal pathways in the central nervous system provides a means of studying the connections of structures deep within the brain without the problems of damage to fibers of passage in anterograde studies or resorting to large lesions in retrograde studies. In this technique, small amounts of radioactive amino acids are injected into the brain and incorporated into proteins by neurons in the vicinity of the injection site. Labeled proteins are transported somatofugally to axon terminals, where they may be subsequently localized by autoradiographic procedures. Since axons do not synthesize protein in significant amounts (Droz and Koenig 1970, Lasek 1970), labeled amino acids are not incorporated by fibers passing through the injection site (Cowan et al. 1972, Crossland et al. 1973). Thus, in the present study the autoradiographic method was used to trace the afferent cerebellar connections of the VA and VL thalamic nuclei and their efferent cortical projections. The results of these experiments will be described and related to the functional organization of the primate motor system.

Methods

Rhesus monkeys were anesthetized with sodium pentothal and mounted in a Kopf stereotaxic head holder. The location of target areas within the cerebellar nuclei and the VA and VL were determined by the atlas of Snider and Lee (1961) and by location of cortical surface landmarks visualized after removal of a large bone flap and dural incision. Injections of the gracile and cuneate nuclei were made under direct vision by incising the atlanto-occipital membrane. Small amounts of tritiated proline (0.1 to 0.5ml) in a concentration of 20 to 30 μCi/μl were injected into the thalamus, dorsal column nuclei, and deep cerebellar nuclei through a 26-gauge needle, fitted to a 1 μl Hamilton syringe. In order to prevent cellular damage and to restrict the size of the injection site, the (^{3}H) proline was delivered slowly by means of a Harvard infusion pump. After the injection, the needle was left in place for at least 20 minutes to avoid contamination of the cortex when the needle was withdrawn.

The animals were sacrificed at survival times ranging from 48 hours to 1 week in order to visualize labeled material in both axon terminals and in axons. The monkeys were reanesthetized and perfused through the heart with 10% formol saline. After further hardening in formalin, the head and intact brain were placed in the stereotaxic apparatus, and the brain blocked transversely in the Horsley-Clark plane or sagittally. The blocks were immersed in sucrose formalin and then encased in a gelatin-albumin mixture. Frozen sections (cut at 30μm) of the entire brainstem, thalamus, and cortex were mounted on gelatinized slides, defatted in xylene and individually coated with NTB-2 (Kodak) emulsion. The slides were exposed at 4°C in light-proof boxes for 6 to 8 weeks, developed in D-19 at 15°C, stained through the emulsion with cresyl violet, and examined with the light microscope under bright-field and dark-field illumination. Chartings of closely spaced individual sections through the injection sites and labeled areas of the brain were made with an overhead projector. Anterior-posterior levels of the brain sections were numbered to correspond with the atlas of Olszewski (1952). Surface reconstructions of the labeled cortical areas were made on enlarged photographs of the cortex.

Results

Afferent connections of the ventral thalamic nuclei

Cerebellar input: Injections of the dentate and interpositus nuclei of the cerebellum were made in five monkeys. The preliminary results will be summarized by describing one case in detail. As illustrated in Fig. 1, the injection site comprises a 2-mm wide strip in the center of the nuclei; it encompasses all but the caudal pole of the dentate-interpositus complex and extends dorsoventrally throughout the entire width of the nuclei. Rostrally, after crossing in the decussation of the superior cerebellar peduncle, labeled axons enter the contralateral thalamus at levels shown in the illustration. Two sharply defined "puffs" of label are located in the central lateral nucleus (CL), and their consistent location throughout serial thalamic sections indicates a precise topography between the lateral cerebellar nuclei and the central lateral nucleus. By contrast, almost no label is found in the centromedian nucleus (CM). Cerebellar axons enter the ventral thalamic nuclei and terminate in VLc (ventrolateral nucleus, *pars caudalis* of Olszewski), in VPLo (ventroposterolateral nucleus, *pars oralis)*, and in VLo (ventrolateral nucleus, *pars oralis*). As shown in Fig. 1, these axonal terminations are concentrated in a band approximately 2 mm wide and located in the most lateral part of the ventral nuclei. This arrangement strongly suggests a precise mediolateral topography in the cerebello-thalamic projections. There are no projections, for example, to the medially located VA or nucleus X. Moreover, cerebellar terminations are not distributed evenly in this narrow strip of thalamus. Rather, silver grains are arrayed in striking bands and semicircular shapes that surround the deeply staining cell clusters of the VL nucleus.

It is also noteworthy that the VPLo receives some of the densest cerebellar terminations. In view of the fact that this thalamic region projects to the motor rather than the sensory cortex (see results in next section), it is important that this rostral part of VPL be further identified as a motor region of the thalamus by virtue of its afferent input from the cerebellum.

Dorsal-column input: In several monkeys, injections of the dorsal column nuclei were made to determine the precise border between the cerebellar and lemniscal recipient regions of the thalamus and to answer the question of whether these motor and

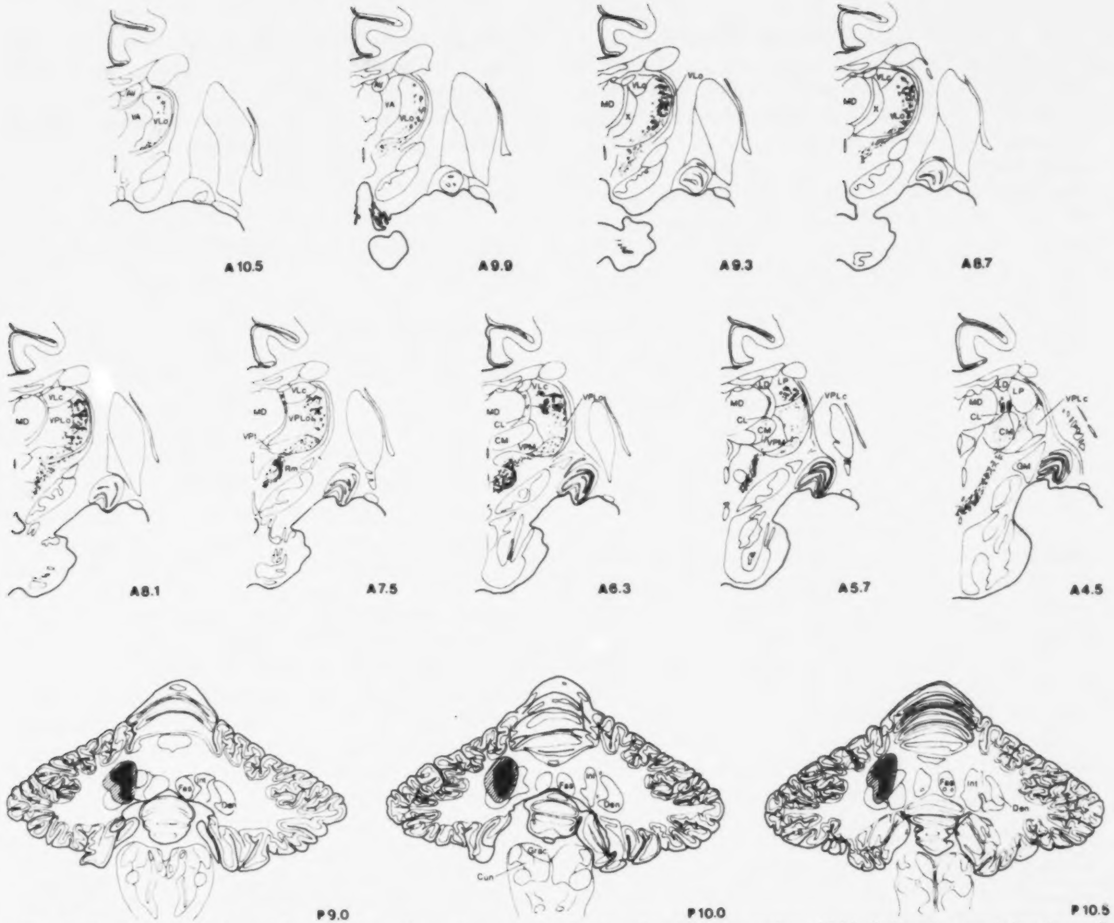

Fig. 1. Series of chartings of coronal sections through the brain of a rhesus monkey (21), following an injection of (^3H) proline into the dentate and interpositus nuclei of the cerebellum. Center of injection site represented by black area; periphery represented by shaded area. Labeled axons represented by broken lines; labeled axonal terminations by stippling. Note horizontal bands of labeled terminals in the VL and VPLo nuclei. Abbreviations used in the figures are as follows: Acc. cun., n. cuneatus accessorius; AD, n. anterior dorsalis; AM, n. anterior medialis; AV, n. anterior ventralis; CL, n. centralis lateralis; CM, n. centrum medianum; Cun., n. cuneatus; Den, n. dentatus; Fas, n. fastigii; GM, n. geniculus medialis; Grac., n. gracilis; Int., n. interpositus ; LD, n. lateralis dorsalis; LP, n. lateralis posterior; MD., n. medialis dorsalis; Pul., n. pulvinaris; R, n. reticularis; S.G., n. suprageniculatus; VA, n. ventralis anterior; VAmc, n. ventralis anterior, pars magnocellularis; VLc, n. ventralis lateralis, pars caudalis; VLo, n. ventralis lateralis, pars oralis; VPI, n. ventralis posterior inferior; VPLc, n. ventralis posterior lateralis, pars caudalis; VPLo, n. ventralis posterior lateralis, pars oralis; VPM, n. ventralis posterior medialis; X, area X.

sensory thalamic regions overlapped to any extent. One such case will be described.

As shown in Fig. 2, the injection site includes parts of both the gracile and cuneate nuclei. Lemniscal fibers are heavily labeled and their terminations are easily identified in the thalamus. In this and other cases, the lemniscal terminations in the ventral nuclear group are confined exclusively to the caudal part of VPL (VPLc of Olszewski). No silver grains are found beyond the VPLc-VPLo border region. Thus, there appears to be no overlap in the cerebellar and lemniscal thalamic inputs.

Efferent cortical connections of the ventral thalamic nuclei

Thalamo-cortical projects of the VA: A number of injections of (^{3}H) proline were made into regions of the ventral anterior nucleus (VA). Two representative cases will be illustrated. In case VA 9 R, the injection site (represented by dark shading) is centered in the VA nucleus (Fig. 3). As shown by the series of chartings, the silver grains representing labeled axonal terminals are found in those regions of the premotor cortex (area 6) occupying the medial wall of the hemisphere and the dorsal bank of the cingulate

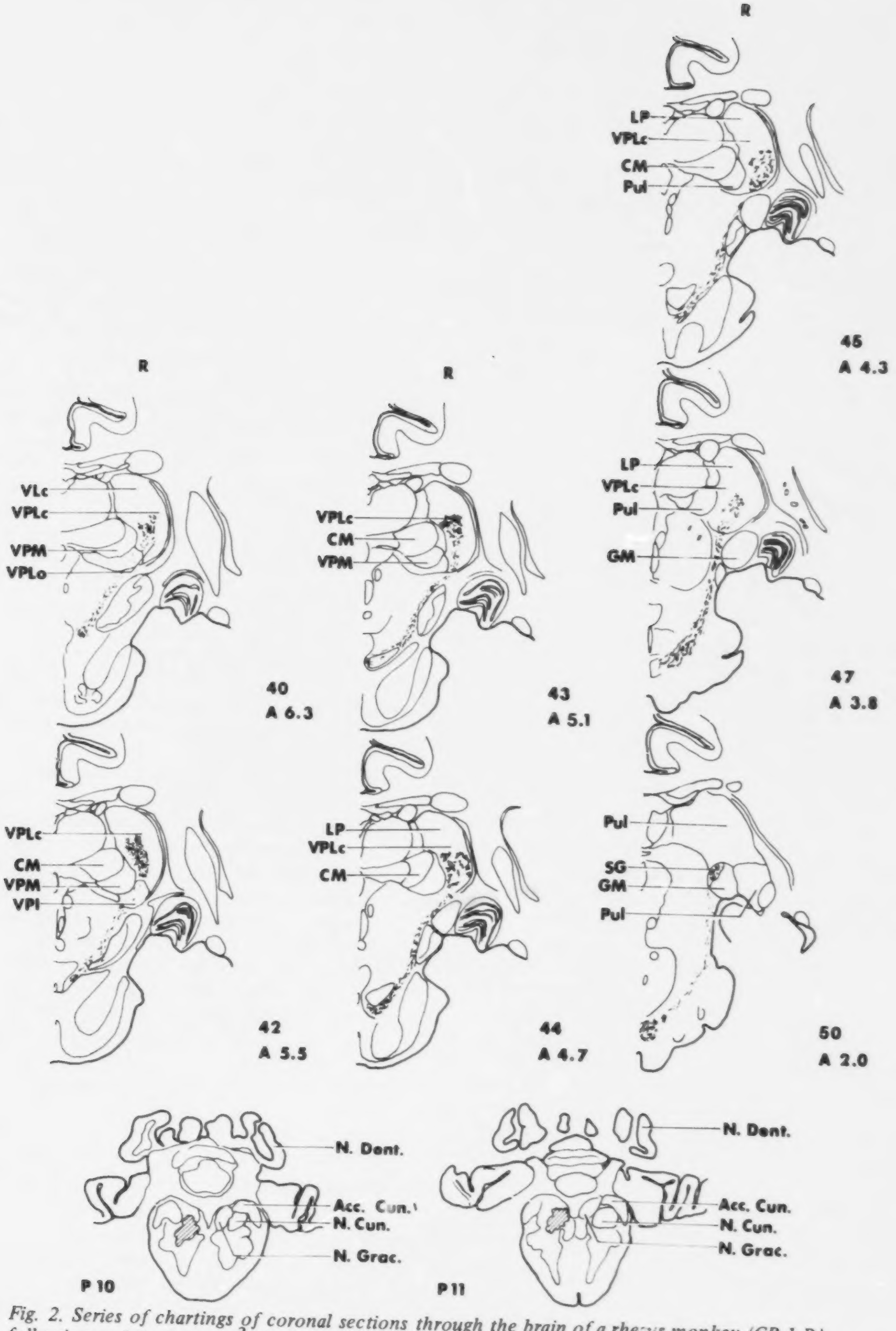

Fig. 2. Series of chartings of coronal sections through the brain of a rhesus monkey (CB 1 R) following an injection of (^3H) proline into the dorsal column nuclei. Injection site represented by shaded area. Labeled lemniscal fibers shown by broken lines; labeled axon terminations in VPLc represented by stippling.

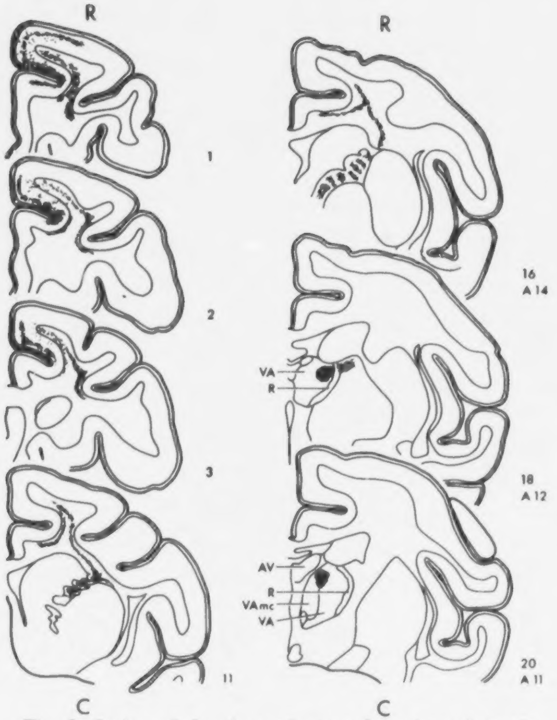

Fig. 3. Series of chartings of coronal sections through the brain of a rhesus monkey (VA 9 R) following injection of (^{3}H) proline into the ventral anterior nucleus (VA). Note terminal labeling in area 6, occupying the medial wall of the hemisphere and the dorsal bank of the cingulate sulcus.

sulcus. (This cortical recipient zone will be reconstructed in Fig. 5.) No fibers from VA terminate in area 4 of the motor cortex. These thalamic afferents to area 6 terminate massively in layer 3. Layers 1 and 6 also contain significant numbers of silver grains.

In another case, VA 3 L, the injection site occupies the VA but also spreads posteriorly into VLc. As shown by the shaded areas in Fig. 4, there is only slight spread of label into VLo. The resultant axoplasmic transport reveals a dense projection to area 6 on the medial wall of the hemisphere and to the cortical surface dorsal to the arcuate sulcus (see reconstruction in Fig. 5). The very sparse projections to area 4 most probably result from the slight labeling of VLo.

When these two cases are compared with other injections of VA, it appears that this thalamic region projects exclusively upon the premotor cortical area 6 in a rough topography such that more anterior levels of the VA project to more anterior regions of area 6. Moreover, on the basis of its cortical projections, VLc appears to be a caudal continuation of VA rather than part of VL, whose cortical association is with area 4 of the motor cortex.

Thalamo-cortical projections of the VL and VPL: In a large number of rhesus monkey brains, localized injections were placed in different areas of the VL and VPL nuclei. In one such case, Monkey VL 1 L (Fig. 6), the center of the injection site was localized in VPLo. Labeled axons stream out of the internal capsule and terminate heavily in the motor cortex (area 4). When these projections are reconstructed on an actual photograph of the brain (as illustrated later in Fig. 9), it is apparent that, although there is some labeling of the somatosensory cortex, the overwhelming amount of label is localized in area 4 of the motor cortex. According to Woolsey's map (1958), the labeled regions of the motor cortex correspond primarily to the face, head, tongue, and a small part of the forelimb areas.

In another case, the injection site is concentrated in VPLo but also extends rostrally into VLo. As shown in Fig. 7, heavy labeling is found in the motor cortex, but despite the fact that a considerable portion of the VPL was labeled by the injection, the somatosensory cortex contains almost no labeled axons. The surface reconstruction (Fig. 8) shows that the labeled areas extend over a broad area of the right precentral motor cortex (area 4), corresponding to the head, face, trunk, and forelimb regions (Woolsey 1958). A careful comparison of reconstructions of a number of VL-VPL injections reveals a topographic projection to the motor cortex such that medial regions of the VLo-VPLo project upon the arm and face areas and lateral regions project upon the leg area.

Precise information was also obtained regarding the projections of the border zones between various regions of the VL and VPL nuclei. The results of many experiments in which small volumes of (^{3}H) proline were injected into the thalamus reveal that injections of rostral VPLo and VLo result in labeling of motor cortex alone, while those centered in VPLc and caudal VPLo reveal a dense projection to sensory areas exclusively. The border zone between these motor and sensory regions is localized in the posterior region of VPLo and the rostral extremity of VPLc. When an extremely small volume (approximately a 1-mm sphere) of this transitionary thalamic region is injected, labeled axons arising from the injection site terminate exclusively upon area 3a in the floor of the central sulcus. This cortex, which receives muscle spindle information (Phillips et al. 1971), is thought to be transitionary between the sensory and motor cortex.

The autoradiographic technique gives extremely precise information regarding the mode of termination of thalamocortical fibers, particularly when the autoradiographs are viewed in dark field illumination. By far the densest termination of thalamic fibers is in lamina 3, a layer containing many medium-sized pyramidal cells and the apical dendrites from the larger

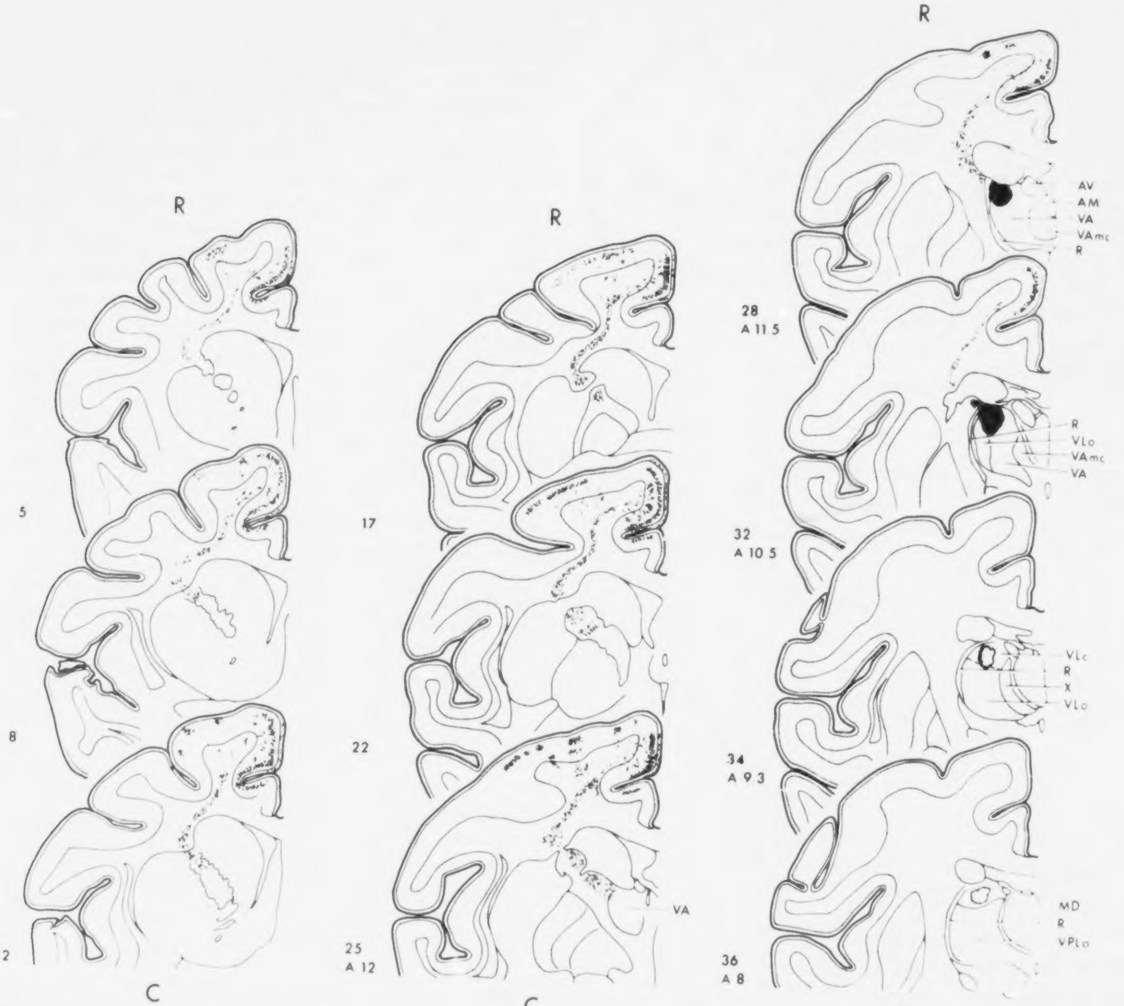

Fig. 4. Chartings of a second case in which proline was injected into VA (monkey VA 3 L). The resultant transport of label to area 6 on the medial wall of the hemisphere and to the cortical surface dorsal to the arcuate sulcus is shown by stippling.

pyramids of layer 5. However, there is also a substantial projection to layer 6. The termination of thalamocortical fibers in layer 1 of the cortex is more variable. In some cases, particularly in the premotor regions, this termination is quite dense, but in other cases (Fig. 9 and 10) there is only sparse labeling of layer 1. Moreover, there is variability in the pattern of thalamocortical axon termination within layer 3. The dark field photo-montage in Fig. 9 shows that the distribution of label in layer 3 of the arm area motor cortex forms a continuous dense band. By contrast, Fig. 10 shows a striking series of columns or patches of label in layer 3 of the face area motor cortex. The bands are about 1 mm in width and are separated by relatively grain-free spaces, about 0.5 to 1 mm wide. These columns also extend into layer 6 of the cortex.

Discussion

The results reported in these experiments reveal that the motor and sensory regions of the monkey's ventral thalamus are separate and discrete. The sensory fibers arising from the dorsal column nuclei terminate primarily upon VPLc and do not extend beyond the VPLc-VPLo border region, which sends efferent fibers to area 3a. This thalamic region corresponds precisely to the areas of VPL in which Poggio and Mountcastle (1963) recorded classical lemniscal responses following stimulation of the periphery. Rostral to this lemniscal recipient zone (i.e., in the region designated by Olzsewski as VPLo), Poggio and Mountcastle described neurons with properties very different from

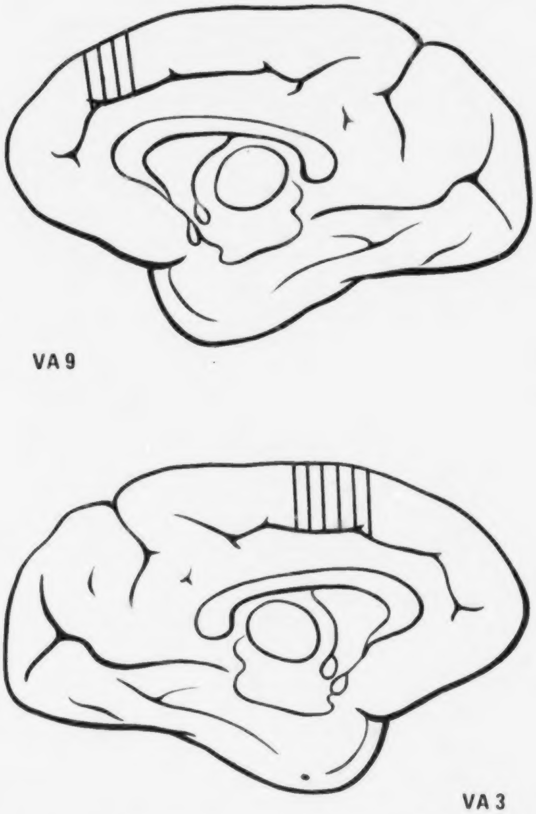

Fig. 5. Surface reconstructions of the medial wall of the hemisphere to show areas of terminal labeling in area 6 of cases charted in Fig. 3 and 4.

the modality-specific lemniscal cells, with their precisely localized peripheral receptive fields. These VPLo neurons were described as having very large or even bilateral receptive fields and were activated only by a heavy or prolonged stimulation of deep tissues. Our experiments reveal a dense topographic termination of efferent fibers from the deep cerebellar nuclei in VPLo, VLc and VLo. These thalamic areas thus represent the motor region of the ventral nuclei. Recent physiological evidence (Strick 1976a) confirms this view since some of these neurons, which are related to arm movements performed by awake monkeys, could not be driven readily by peripheral afferent input. Thus, the present anatomical findings show that motor and sensory inputs to the thalamus do not overlap, and these results are strongly supported by physiological experiments.

Similarly, the efferent thalamocortical connections of the ventral nuclear complex reveal a topography and clear-cut demarcation among (1) VA and VLc projecting to the premotor cortex (area 6), (2) VLo and rostral VPLo projecting to the motor cortex (area 4), (3) a VPLo-VPLc border zone projecting to area 3a, and (4) caudal VPLo-VPLc projecting to the somatosensory cortex. Again, there is no overlap in the motor and sensory thalamocortical fiber systems. These results are supported, in part, by the retrograde horseradish-peroxidase method used by Strick (1976b), who also found that a large rostral zone of VPL (i.e., VPLo) projects not to sensory but to motor cortex. This finding raises the question as to whether this region of the thalamus is actually part of the VPL receiving peripheral afferent input or whether it is, in fact, a caudal region of VL that has heretofore not been identified correctly. The issue of whether the motor cortex receives somatosensory input directly from the thalamus is especially significant in view of the recent observations by Rosen and Asanuma (1972) that cortical efferent zones in the monkey's motor cortex, which influences distal forelimb muscles, receive a projection from cutaneous afferents. These authors concluded that cooling of the postcentral gyrus showed that sensory cortex was not involved in transmitting peripheral input to the motor cortex and that "the thalamic region of origin for the fibers subserving peripheral afferent input to the motor cortex is obscure." Our anatomical results clearly show, however, that VPLo does not receive lemniscal input from the dorsal column nuclei but is, instead, a cerebellar recipient zone. Thus, physiologically demonstrated peripheral afferent input to the motor cortex must travel by routes other than the classical lemniscal pathway.

More recently, Lemon and Porter (1976) and Lemon et al. (1976) have reinvestigated the correlation between peripheral afferent input and movement-related neurons in the motor cortex of awake behaving monkeys, rather than in the anesthetized preparations used by Rosen and Asanuma. Lemon and Porter found that the most powerful peripheral input to the motor cortex was generated by joint movement. This input probably originates in muscle, tendon, or joint receptors, but the receptors could not be specifically identified in these experiments. The brevity of the latencies reported in these studies argues for a fairly direct projection from the periphery to the motor cortex, but the authors conclude that neurons in VL are unresponsive to peripheral inputs or have poorly localized responses and that VPL and its fast afferent pathways are a more likely route for peripheral afferent input to the motor cortex. This conclusion accords well with the anatomical data reported here, i.e., that the VPLo receives a massive cerebellar input that is then relayed directly to the motor cortex. However, the "fast afferent pathways" to VPL must come from the cerebellar nuclei and not the dorsal column nuclei.

Regarding the columnar organization of the motor cortex, Rosen and Asanuma (1972) suggested that afferent input is topographically organized such that each motor cortical "column" receives a specific

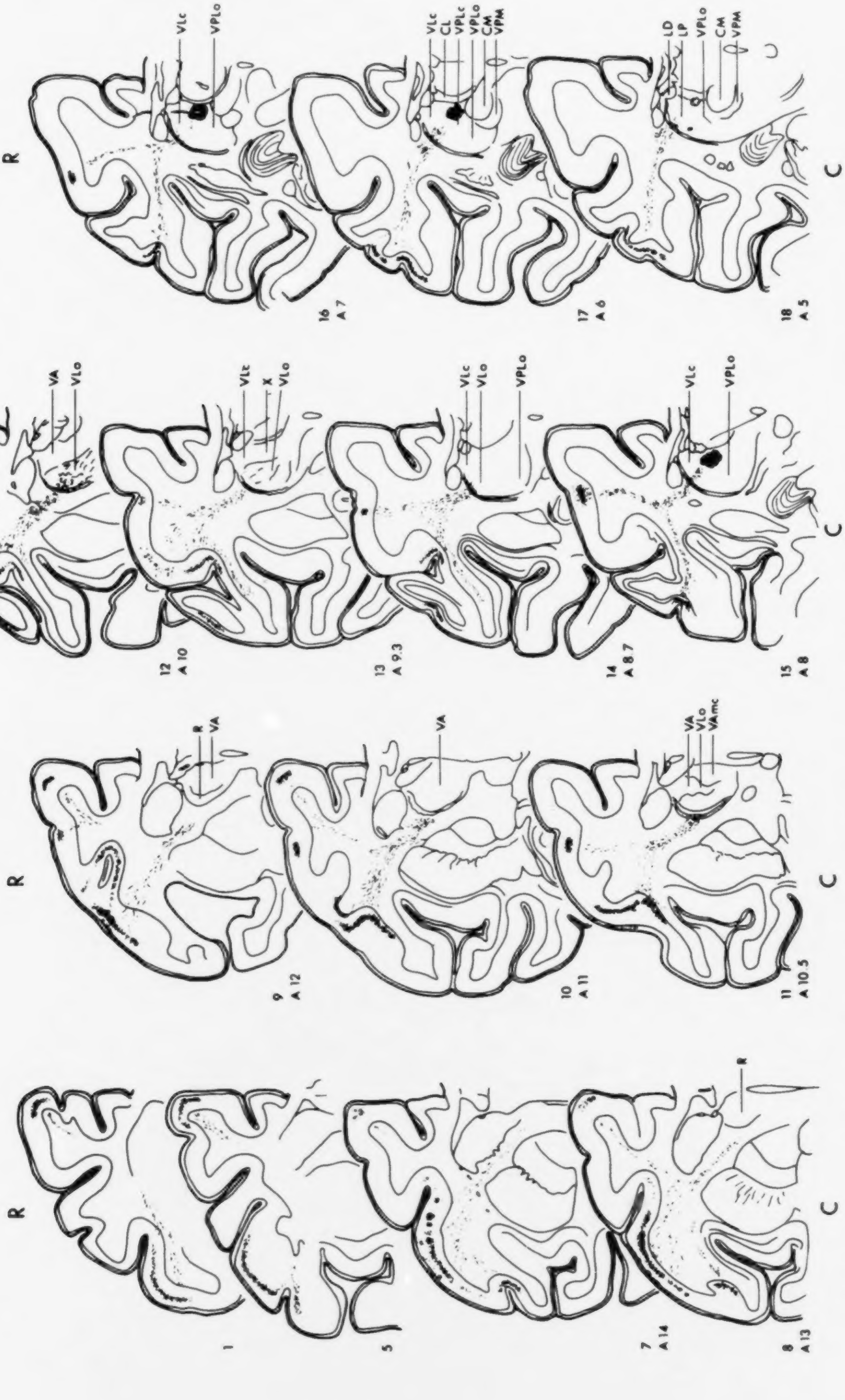

Fig. 6. A series of chartings of coronal sections through the brain of a rhesus monkey (VL 1 L) following injections of (^3H) proline into VPLo of the thalamus. Terminal labeling (represented by stippling) is heaviest in the motor cortex, area 4, and is concentrated in layer 3. Labeled axons also terminate in the somatosensory cortex.

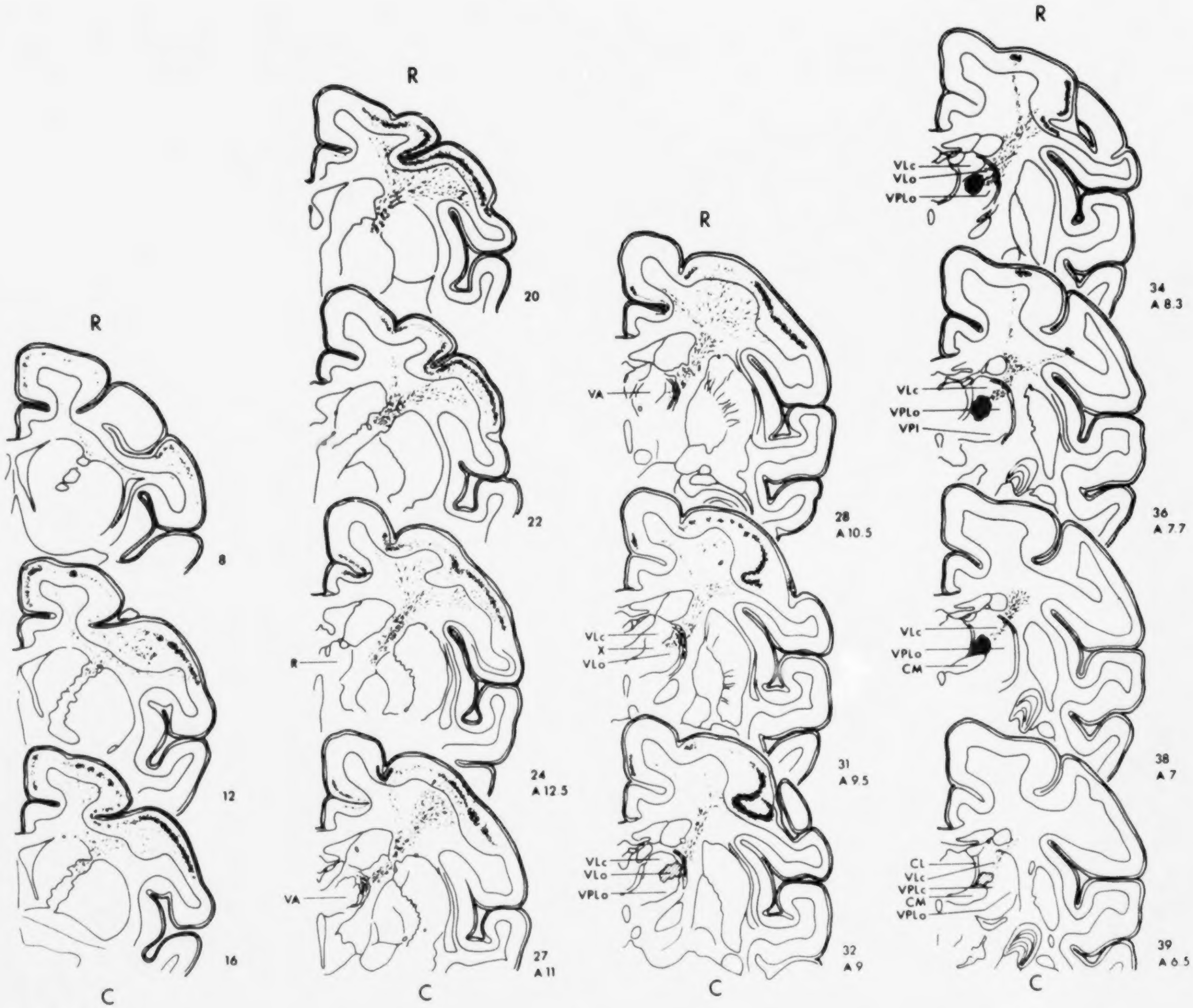

Fig. 7. Chartings of coronal sections of a brain with injection of (^{3}H) proline into VPLo and VLo. Heavy labeling is found in the motor cortex but almost none in the somatosensory cortex.

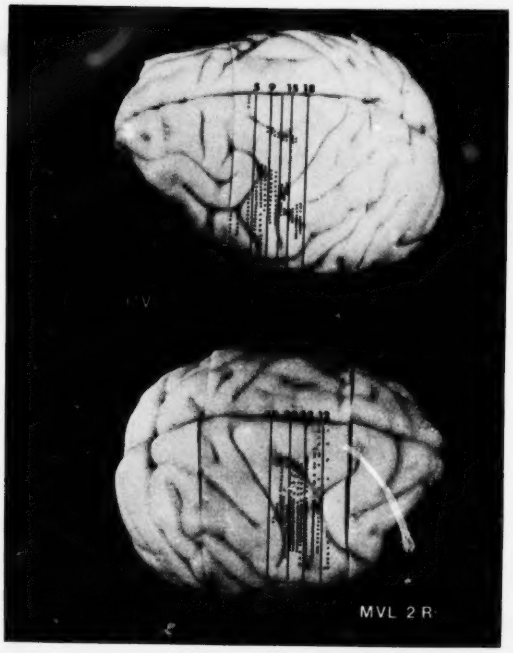

Fig. 8. Surface reconstruction of cases plotted in Fig. 6 and 7. Dots on brain photographs show labeled areas extending over broad areas of the precentral motor cortex (area 4), with relatively little labeling of the somatosensory cortex from injections of the VL-VPL nuclei.

peripheral input from the same anatomical zone to which the column projects. By contrast, the experiments of Lemon and Porter (1976) on awake behaving monkeys suggest a less rigid arrangement of the afferent projection since a local region of the motor cortex may receive inputs from entirely different joints. These authors conclude that "there is no highly specific columnar organization of cells within the motor cortex, divided and separated one column from the other, either from the point of view of the afferent input to these cells, or from the point of view of the motor activities with which the discharges of the cells are associated."

On the basis of the physiological data of Lemon and Porter, it seems unlikely that "puffs" of label found in layer 3 of the face area of the motor cortex after injection of the VPLo represent physiological "columns." It seems more likely that "puffs" of high grain density represent the terminations of thalamocortical projection fibers and that the grain-free spaces are filled in by commissural fibers from the other hemisphere. If this interpretation is correct, the cortical areas representing the arm and leg receive a continuous band of thalamocortical fibers since cortical regions serving distal extremities would not receive commissural fibers.

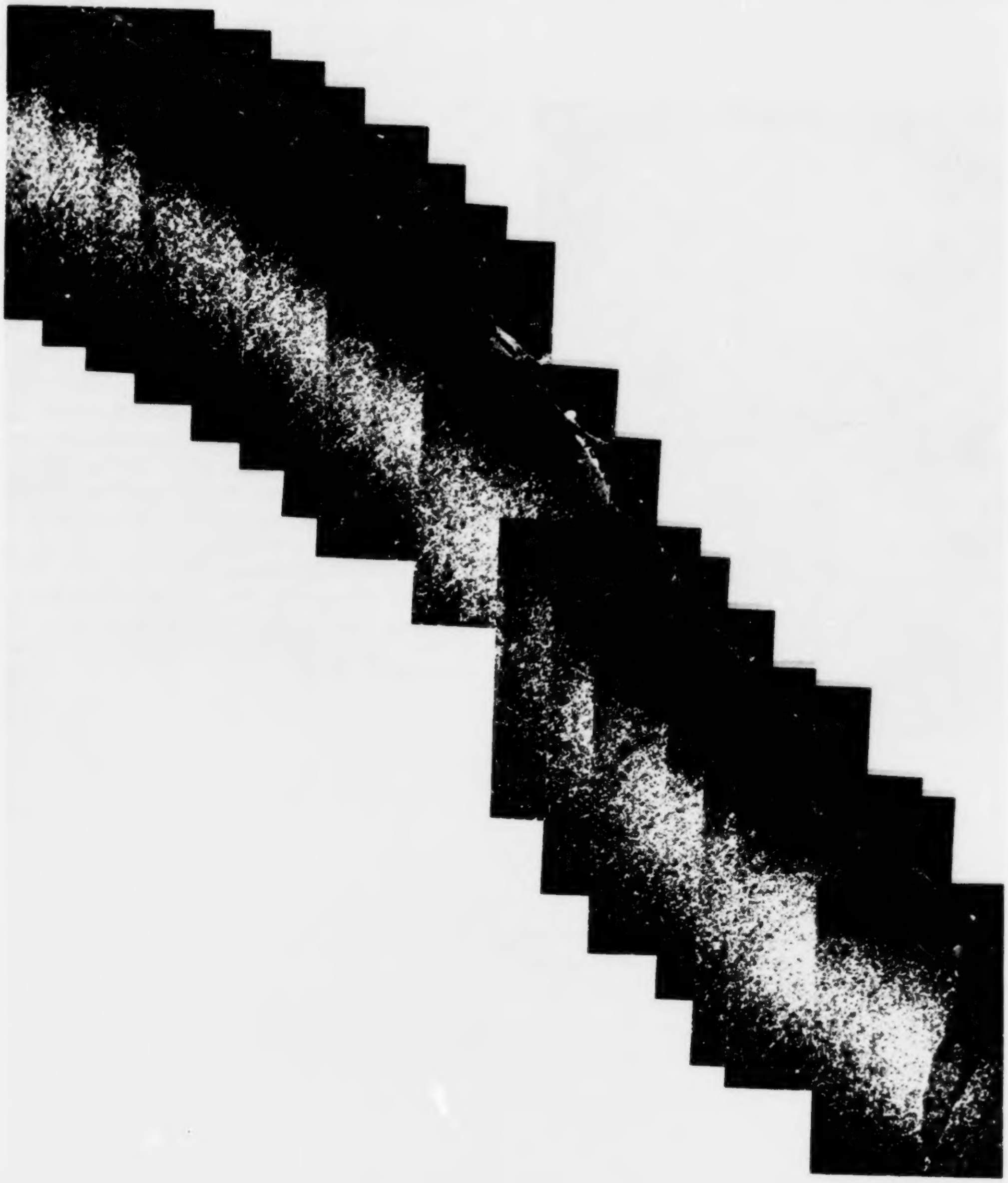

Fig. 9. Dark field photo-montage shows distribution of label in layer 3 of the arm area motor cortex. Note that the label forms a continuous dense band, which appears white in dark-field.

Fig. 10. Dark field photo-montage shows series of columns or patches of label in layer 3 of the face area motor cortex. The bands are about 1mm in width and are separated by relatively grain-free spaces about 0.5 to 1 μm wide.

RELATIONSHIPS BETWEEN BEREITSCHAFTSPOTENTIAL AND CONTINGENT NEGATIVE VARIATION

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The Bereitschaftspotential (BP), or readiness potential, and contingent negative variation (CNV) were discovered independently, and first reported in 1964. The term BP is generally reserved for cerebral slow potential changes preceding a voluntary action, while the term CNV is most frequently applied to slow potential changes occurring in the interstimulus interval of a foreperiod reaction time situation. Both are electrically negative phenomena at the surface of the cerebral cortex, over which they are widely distributed, and both appear in circumstances involving preparation for action or decision. The tendency in the past to speak of the CNV as if it were a simple unitary phenomenon may have been misleading. Two or more relatively independent components emerge in certain circumstances. Loveless and Sanford (1973) and Loveless (1976) suggest that the late negativity of the CNV–i.e., that part which immediately precedes the imperative stimulus–may be identical with the BP and distinct from earlier negativity associated with the warning stimulus, a view supported by Rohrbaugh et al. (1976). Others suggest that the two effects may be manifestations of activity in the same underlying systems. Before such issues can be resolved, it is necessary to take a closer look at what relationships can be observed between the BP and CNV.

As a result of collaborative work between the groups responsible for the discovery of both potential changes, an experimental paradigm and computer programs were evolved to examine the form and distribution of the two potentials separately and jointly. This procedure was demonstrated by Deecke and his colleagues at Bristol (McCallum and Knott 1976). This paradigm has been modified and extended in the present experiment to further investigate the relationship involved.

Method

Scalp recordings were made from 12 normal subjects (8 female, 4 male) using Ag/AgCl electrodes. Similar cortical recordings were made from 12 patients (9 female, 3 male) in whom gold electrodes had been implanted in connection with clinical procedures.

Recording was by a modified 16-channel Elema Schonander Mingograph linked to a PDP-12 computer. Time constants of 5 sec were used for normal controls and, where possible, for the patient group. In the latter group, however, it was necessary in five cases to reduce the time constant to 2.5 sec and in five cases to 1.2 sec to offset the effects of high-amplitude infraslow activity, to which the intracerebral electrodes become increasingly sensitive. Scalp electrodes were located at 2 cm above the nasion, F3, F4, C3, Cz, C4, P3, and P4, and referred to a common reference consisting of the linked mastoids. Cz was compensated for eye movements as described by McCallum and Walter (1968). Individual trials contaminated by eye movement or other artefacts were rejected on-line. Recording in the patient group was from eight selected subdural gold electrodes, each 150 μm in diameter and 4 mm long, extending in an anterior-posterior line over the right cerebral cortex from the prefrontal region to the postcentral gyrus. Surface Ag/AgCl EMG electrodes were located over the flexor muscles of the right and left forearms in normal subjects and patients.

The basic task consisted of pressing, with the index finger, a 1-cm-diameter metal stud, housing a pressure transducer, set in a flat wooden base. All subjects reclined on a bed with eyes open and fixated. The experimental procedure consisted of a BP condition in which subjects made brief, voluntary finger presses with a minimum interval of about 10 sec between presses. Twenty-four presses were sampled from the left hand and 24 from the right. For all conditions, the epoch sampled was 4 sec at a rate of 128 Hz. Two seconds were sampled before and 2 sec following each trigger pulse. The trigger pulse was initiated from the output of the pressure transducer. The second, or CNV, condition consisted of a foreperiod reaction time (RT) situation in which a single warning click, delivered 2 sec after the start of the sampled epoch through headphones at approximately 70 dB, was followed 1.5 sec later by a 700-Hz tone terminated as rapidly as possible by pressing the metal stud with the index finger of the preferred hand (or the left hand in the case of the patient group). RT was automatically recorded by the computer. Finally, in a BP/CNV condition, the two situations were combined, the click stimulus being removed. Subjects made a series of voluntary button presses with the preferred hand (normals) or left hand (patients). Each press was followed 1.5 sec later by the tone which subjects were required to terminate as rapidly as possible by a second button press, with the same finger. BP and CNV amplitudes were measured with respect to a baseline calculated as the mean amplitude of activity recorded during the first 300 msec of the sampled epoch.

Results

Both BPs and CNVs were present in all subjects and patients and, superficially, showed a similarity of distribution. Both were largest at the vertex, the mean scalp amplitude for Cz being - 12.5 μV for CNV and -5.0 μV for BP. As in previous studies, scalp CNV showed no consistent asymmetry in its distribution. Individual differences between bilateral pairs of electrodes could be up to 3μV, but these were not consistent in direction across the group, nor did they appear to be related to handedness or to the task involved. Scalp BP showed a small asymmetry, amplitude values over the hemisphere contralateral to the hand used for pressing being slightly higher than those over the ipsilateral hemisphere (Table 1). Differences for left-hand presses failed to reach significance, but those for right-hand presses were significant for central ($p<.05$) and parietal ($p<.01$) locations using a t-test for correlated samples.

Both BP and CNVs were smallest over the frontal and prefrontal regions, and the BP frequently could not be observed at all in these areas. The CNV, however, was almost invariably observable frontally, if only at low amplitude. In the combined BP/CNV condition (Fig. 1), scalp CNV diminished by up to 30% over central and 20% over parietal areas compared with the standard CNV condition (Table 1), but remained relatively unchanged over frontal areas. In the same condition (BP/CNV), scalp BP showed increases of 30% or higher over all areas (including frontal) compared with the simple voluntary press condition. Fig. 2 presents cross-subject vertex averages for the four conditions.

Anterior-posterior CNV distribution over the right cortex of patients was similar to scalp recordings in normal subjects with the largest amplitudes found precentrally. In some patients the most anterior electrodes showed no CNV, while in others the CNV was quite prominent there, but varied somewhat in form. BP amplitudes were markedly diminished when the ipsilateral hand was used for pressing. Fig. 3 shows this asymmetry in one patient. In the one left-handed patient, this difference between contralateral and ipsilateral hand presses was even more pronounced. BP distribution also spread more anteriorly in this patient. Fig. 4, which illustrates waveforms from the eight selected electrodes averaged across patients shows the consistency of the asymmetry. Fig. 5 provides similar across-patient averages for the CNV and BP/CNV conditions. The locations of electrodes varied to some extent from patient to patient, although the most anterior electrode was always over prefrontal cortex; the second electrode was always over frontal cortex; and the remaining electrodes extended posteriorly from precentral cortex, the most posterior electrode usually being over the postcentral gyrus. The distance of electrodes from the midline also varied considerably. This variability and time constant differences are ignored in Fig. 4 and 5 to obtaining a broad picture of hemispheric differences. Therefore, these summary averages should not be taken as a reliable indication of localized differences of waveform or amplitude, although individual records clearly indicate that such differences exist.

Table 1. Mean Amplitude (μV) of the Bereitschaftspotential and CNV on the Scalp in Different Tasks

	Electrode position							
Measure (task)	Above nasion	F3	F4	C3	C4	Cz	P3	P4
BP (left)	-1.82	-1.55	-1.36	-3.18	-3.45	-5.27	-2.0	-2.09
BP (right)	0	-0.91	+0.45	-3.64	-1.45	-4.55	-1.3	0
BP (combined)	-1.1	-2.9	-1.7	-4.8	-2.7	-6.0	-2.6	-1.4
CNV (simple)	-0.7	-4.1	-4.5	-8.2	-8.2	-12.5	-6.1	-6.1
CNV (combined)	-1.3	-4.3	-4.0	-6.7	-6.4	-8.5	-5.4	-5.0

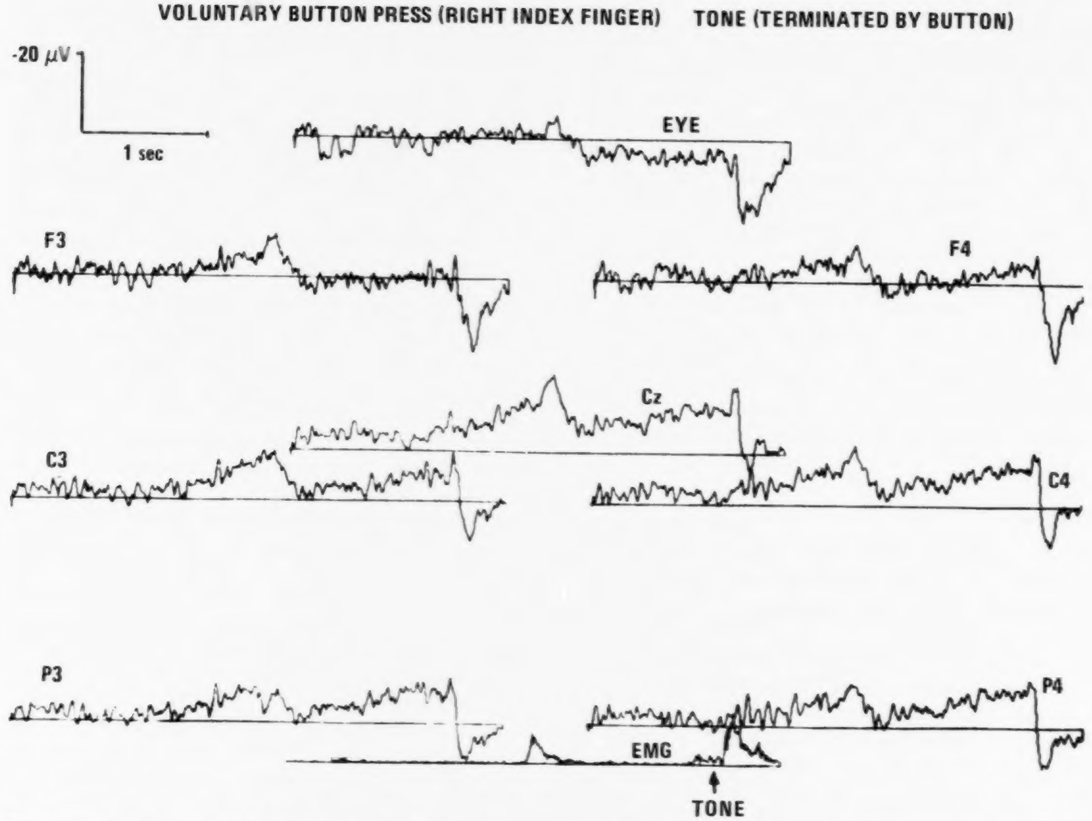

Fig. 1. Scalp distribution of the combined BP/CNV condition from one normal subject. Averages of 24 trials in which subject made a voluntary right index finger press, followed 1. 5 sec later by a tone, terminated by a second press using the same finger. ·

Mean RT to the imperative stimulus in the standard CNV condition was 160 msec (SD 40) in normals and 185 msec (SD 50) in patients. In the BP/CNV condition, these values increased to 185 msec (SD 52) for normals and 224 msec (SD 71) for patients. Differences between the conditions were significant for both groups on a t-test for correlated samples ($p<.05$).

Discussion

Results indicate that BP is maximal at the vertex and is weakly asymmetrical, showing increased negativity over the hemisphere contralateral to the operative muscles, the largest values occurring prerolandically. The asymmetry appears most marked when the dominant hemisphere is the one primarily involved in the movement. This finding is consistent with that of Kutas and Donchin (1974) and is in general agreement with that of Deecke et al. (1973), although the latter authors wish to differentiate between several separate components in the activity preceding motor movement.

Intracerebral data confirm the distribution pattern that emerges from scalp data. The fact that cortical electrodes in any one patient were restricted to one hemisphere prevented bilateral comparisons, but the differences seen in response to left- and right-hand pressing reveal the contralateral predominance of the BP more clearly than scalp data.

As indicated in Table 1, mean CNV amplitudes for the normal group were remarkably symmetrical. This finding is consistent with those of McCallum and Cummins (1973), McCallum (1976), and Marsh and Thomson (1973). Isolated reports of CNV asymmetries under special conditions have appeared, which might seem to contradict the established view (Low et al. 1966, Cohen 1969) that CNVs are bilaterally symmetrical. Otto and Leifer (1973b) reported larger negative shifts over the motor cortex contralateral to the movement, but the measure used was total CNV area and the differences only reached significance when pooled to include a condition in which a motor response was initiated during the S1-S2 interval. Butler and Glass (1974) have observed larger CNVs over the dominant hemisphere during numeric operations, but the findings have not been replicated. Low et al.

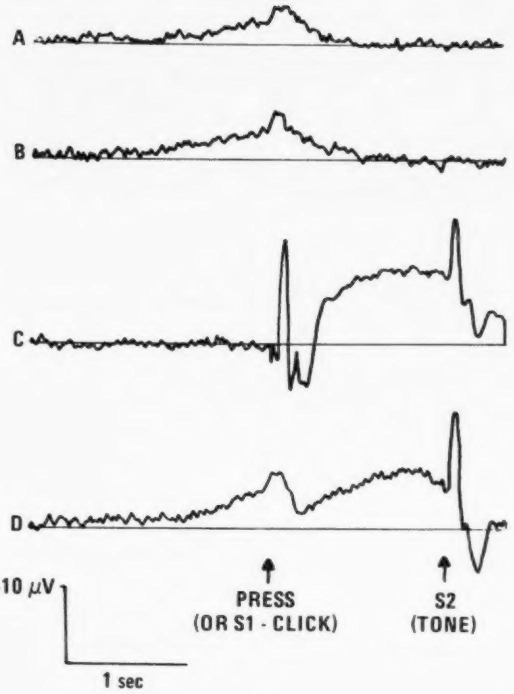

Fig. 2. Averages (12 subjects) of vertex (Cz) channel for each of the four experimental conditions. A: Voluntary press, left index finger; B: Voluntary press, right index finger; C: CNV–click, tone, button press with index finger of preferred hand; D: BP/CNV (as in Fig. 1).

(1976) also reported mean CNV area asymmetries related to hemispheric dominance for language production in patients and to handedness in normals. The extent to which they apply to "late" negativity, however, is not clear. So far, the balance of evidence does not substantiate any claim for consistent asymmetry of CNV amplitude measured prior to the imperative stimulus.

Although superficially similar, the BP and CNV are independent in terms of distribution and the balance between the two distributions varies with the situation. Results of the present study further suggest that, as task involvement increases, frontal areas make a relatively greater contribution, as reflected in the distribution of both types of slow potential change. In planning future ERP experiments to examine the role of different cerebral regions in the context of planned motor actions, the value of adding levels of task complexity or involvement to the simple press or warned foreperiod situation should thus be considered. (See also Papakostopoulos, this section.)

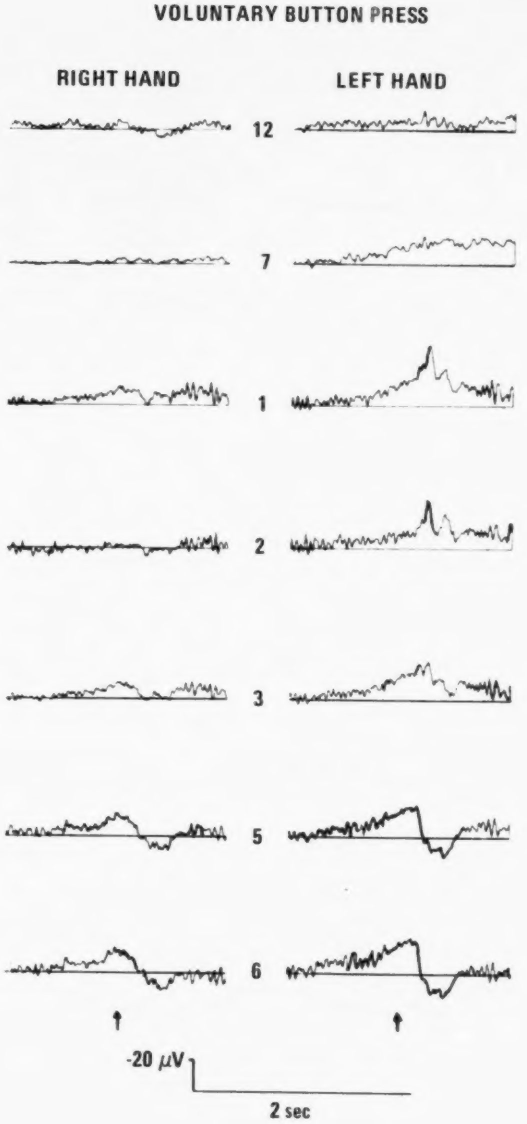

Fig. 3. Anterior-posterior cortical distribution of BP over the right hemisphere of one patient, recorded from gold subdural electrodes extending from prefrontal (electrode 12) to postcentral (electrode 6) regions. Averages of 24 trials.

While this study underlines the inappropriateness of speaking of the CNV as if it were immutable in form and distribution, it lends little support to those who, rejecting a "unitary phenomenon" theory of

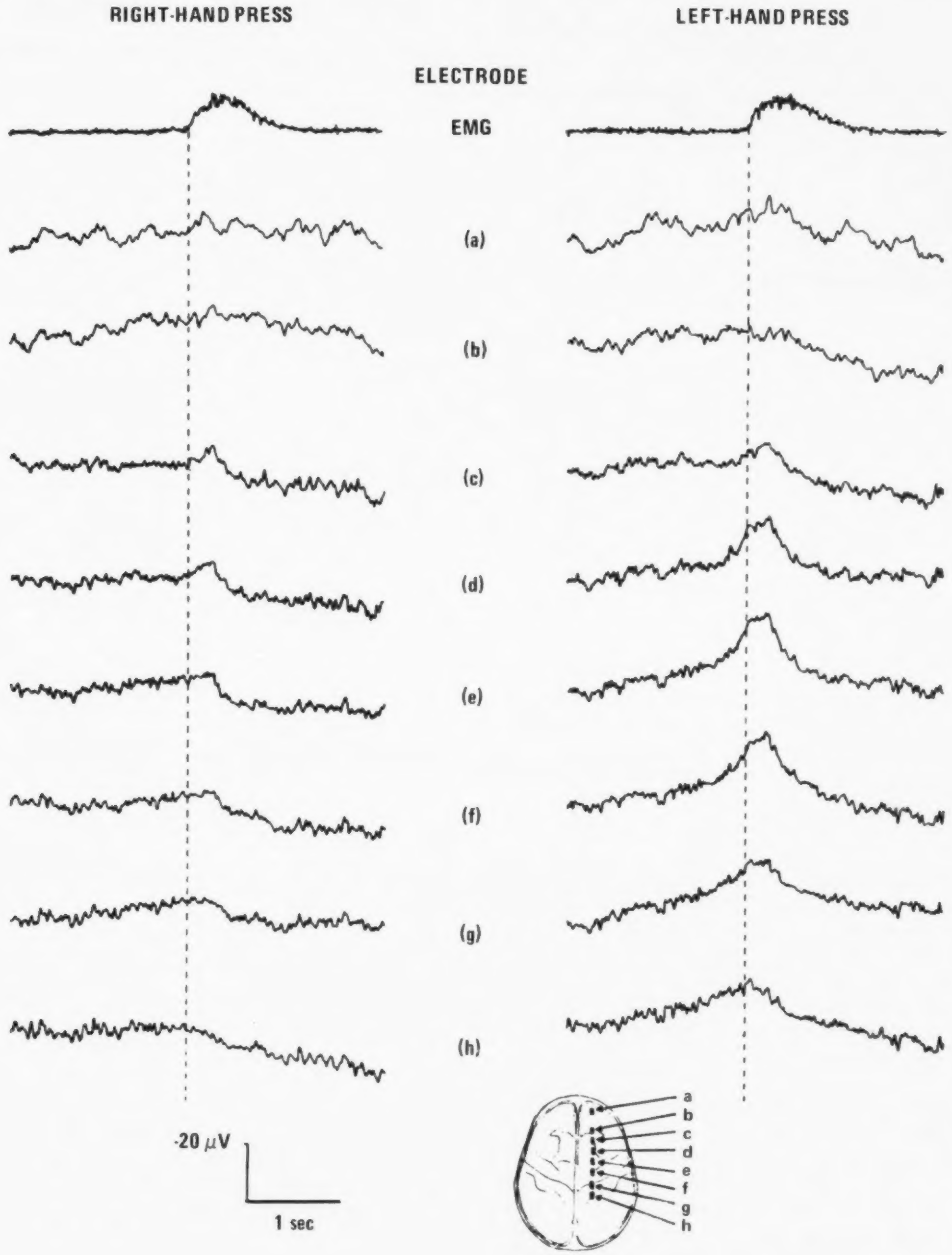

Fig. 4. Averages (eight patients) from an anterior-posterior line of gold subdural electrodes over the right hemisphere for BP conditions involving left and right voluntary finger presses. Note: The diagram showing electrode placement gives only a general indication of their distribution. Exact locations of equivalent electrodes varied from patient to patient. These differences have been ignored in averaging.

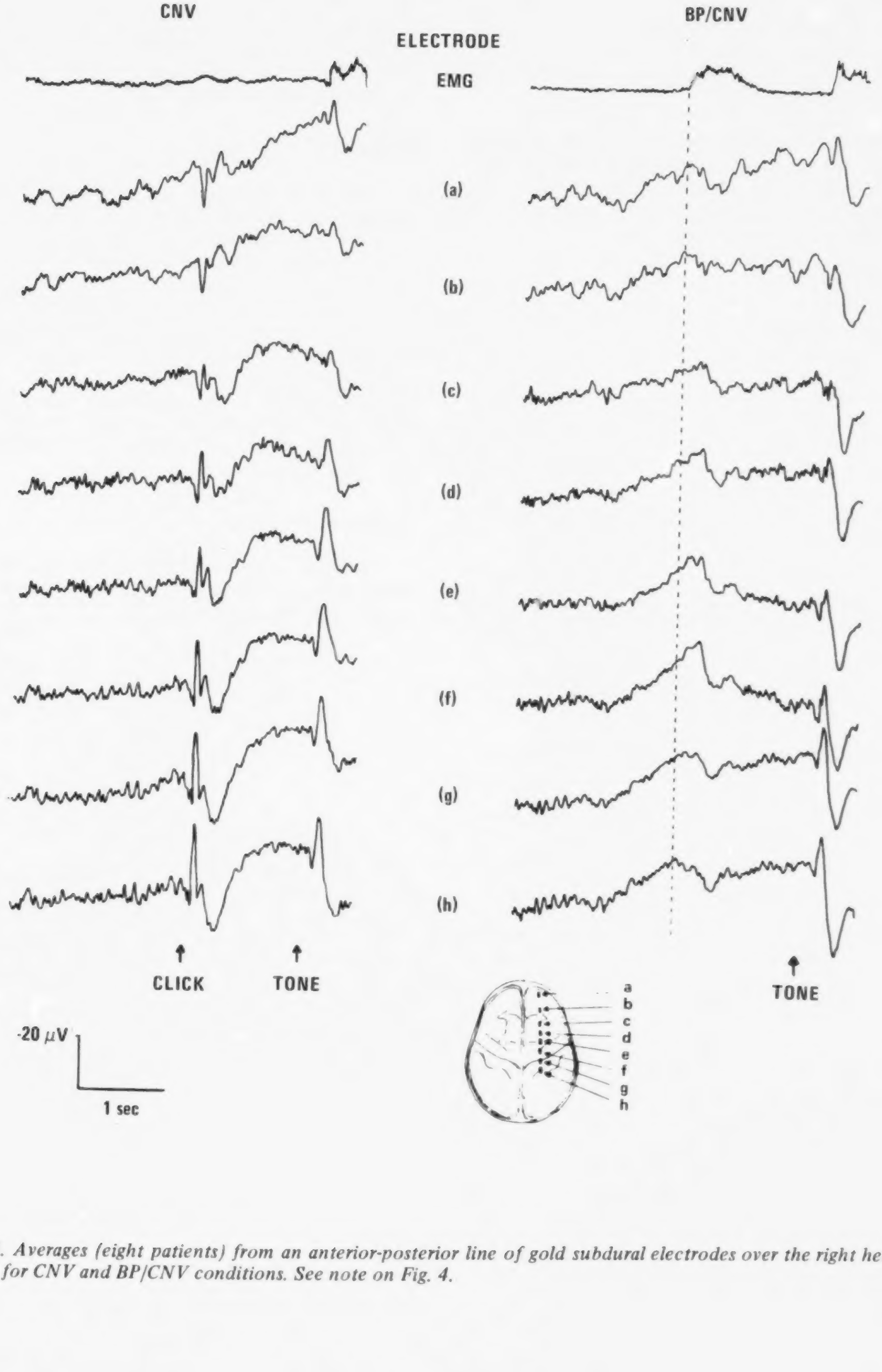

Fig. 5. Averages (eight patients) from an anterior-posterior line of gold subdural electrodes over the right hemisphere for CNV and BP/CNV conditions. See note on Fig. 4.

CNV, seek to replace it with a two-, three-, or multicomponent theory. To equate early CNV negativity with an orienting response when it can be seen to occur–albeit slightly diminished–when S1 is replaced by a voluntary button press, is at best an oversimplification. To equate late CNV negativity with the BP is also an oversimplification because a clearly lateralized BP and symmetrical CNV can be demonstrated at the same electrode sites.

Mounting evidence points to slow potential changes as a function of an extensive mosaic of cortical neuronal domains. Which domains are active during a particular process of preparation for action or decision and at what time during the course of that preparation they are active will depend upon innumerable factors inherent in both the individual and the situation. Intracerebral recording reveals some of the resultant subtle changes and local differences. Few of these subtleties, however, survive the spatial averaging that takes place in the transition through skull to scalp. Variations in the distribution of waveforms seen at the scalp can hopefully provide information on broad areas of function and can indicate cortical regions primarily involved at given points in time. However, it seems unwise to be lured into a process of component labelling on the basis of sparsely sampled scalp data acquired in a limited range of circumstances. Hastily applied labels, particularly those derived from broad psychological constructs, add little to our understanding of brain events and may even impose constraints on our thinking and interpretation. It would be wiser to review some of the constructs concerned in the light of recent event-related potential data than to squeeze the physiological data into ill-fitting psychological or behavioural categories.[1]

Summary

Bereitschaftspotential and contingent negative variation were recorded independently and in association with one another from multiple scalp electrodes in a group of normal subjects and from subdural electrodes over the right hemisphere in a group of patients. The distribution of the two phenomena was similar, but not identical. CNV was slightly more prominent anteriorly than BP, and BP showed some asymmetry–largest over the hemisphere contralateral to the hand used in pressing. In the situation in which BP and CNV were combined, BP appeared frontally and increased in amplitude at all electrodes, whereas CNV decreased over central and parietal areas.

Acknowledgment

The help of Philip Newton in recording data and Philip Pocock in development of the computer program is gratefully acknowledged.

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[1] Ed. note: See D. Papakostopoulos, "Macropotentials as a Source for Brain Models," Section X, this volume.

SLOW POSITIVE SHIFTS DURING SUSTAINED MOTOR ACTIVITY IN HUMANS

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Bates (1951) was the first to report slow cortical potentials associated with movement onset. He described a negative shift commencing about 20 msec after EMG onset and attributed the wave to the "arrival of afferent impulses from the periphery." Bates failed to detect any cortical potentials preceding movement. Kornhuber and Deecke (1965), using improved averaging techniques, observed a slow negative shift before movement, followed by a positive shift after movement onset. Vaughan et al. (1968) designated this late positive wave as the P2 component of the motor potential. Since the late positive wave appears to follow the initiation of motor activity, Kornhuber and Vaughan both hypothesized a peripheral afferent origin. The evidence, however, is inconclusive.

Otto et al. (1977) observed a prolonged positive shift, maximal postcentrally, during sustained motor response. In that study, subjects were required to estimate the duration of a 1-sec holding interval without external cues. It is possible, therefore, that the positive shift reflected a central timing mechanism, rather than afferent input from peripheral muscles. This hypothesis may be tested by estimating time without sustained motor response. On the other hand, if the positive shift represents incoming afference, one would expect to see larger shifts over the sensorimotor region contralateral to response. Further, one would expect to find the amplitude of positivity directly proportional to the force of contraction. The present study was undertaken to test these hypotheses.

Method

EEG recordings, referred to linked ears, were obtained from nine young adult male subjects at C3, C4, P3, and P4 using amplifiers with 2.25-sec time constants. EOG and rectified EMG from the brachioradialis muscle were also recorded. A Schmitt trigger, adjusted to fire at EMG onset, was used to synchronize signal averages. Each subject's maximal pressing force, with the dominant hand, was determined with a Jamar PC5033 hand dynamometer. Each subject then completed a series of 3-sec contractions at force levels of 10, 25, and 50% maximum, as monitored visually on the gauge of the dynamometer. Subjects were instructed to initiate and terminate contractions briskly and to relax responding muscles as completely as possible between presses.

Two additional conditions were run to determine the effect of estimating time *without tonic contraction* and the corollary effect of tonic contraction *without estimating time*. The estimation task consisted of squeezing the dynamometer briefly to indicate the lapse of 3-sec after presentation of a tone pip. In the nonestimation task, subjects initiated and maintained contraction until presentation of a tone pip.

Results

Prolonged positive shifts were observed during hand pressing in most subjects in most conditions. Averaged waveforms recorded in six subjects during the 50% condition are shown in Fig. 1. Positive shifts during pressing were easily discernible in the raw data of many subjects, as shown in Fig. 2. This sample illustrates, however, that the positive shift is not invariably present, nor is the onset and termination clearly time-locked to activity in the brachioradialis muscle.

Fig. 3, averaged across subjects, illustrates that the magnitude of positivity is not directly related to pressing force at C3 and C4. Larger shifts were observed during the 10% and 50% conditions than during the intermediate 25% force level. Only at P3 was there a suggestion of a linear relationship between amplitude and force. No consistent laterality differences were observed in any condition.

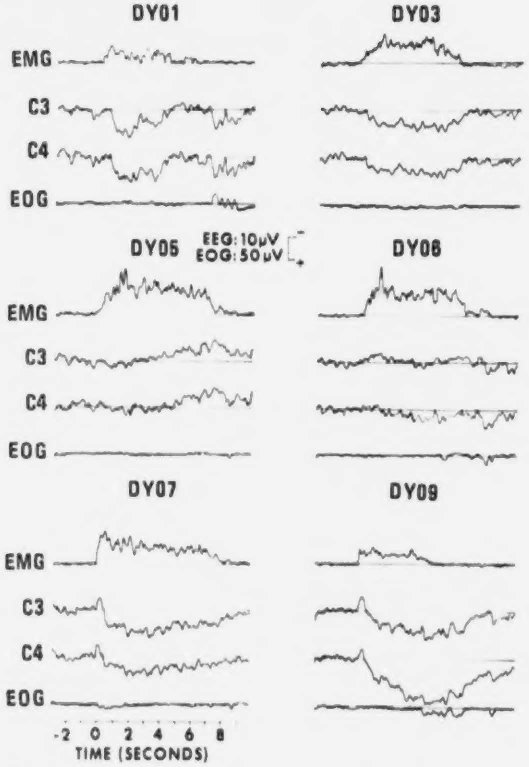

Fig 1. Slow potential shifts observed in six subjects during 50% isometric contraction. Averages of 6 to 11 trials were triggered from onset of brachioradialis muscle EMG and digitized at 48 msec/point by means of a PDP-12 computer. EOG was recorded diagonally from above the inner canthus to below the outer canthus of the right eye. Baseline was computed from the initial 400-msec segment in each average.

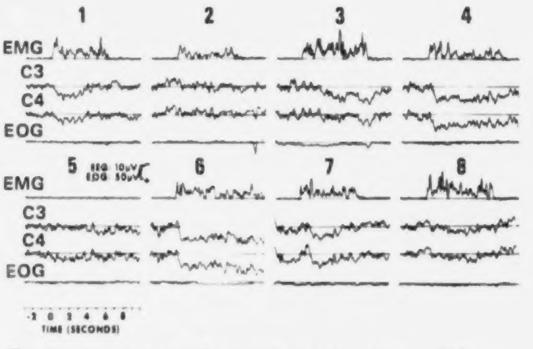

Fig 2. Single trials from one subject during 50% contractions. Note that positive shifts are not present in all trials or clearly time-locked to the firing onset or offset of the brachioradialis muscle. Trial 5 was triggered from a transient EMG spike. Trials with improper EMG triggering, or EOG artifact, during or preceding contraction were excluded from averages.

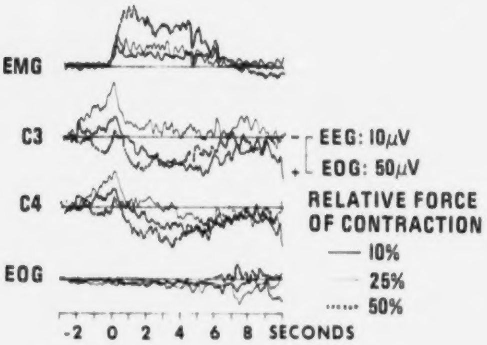

Fig 3. Composite averages from seven subjects during 10%, 25%, and 50% contractions. Positive shifts do not appear to be proportional to force of contraction.

Results of the delayed response task (labeled SR) provide evidence that the positive shift during sustained motor activity is not the reflection of a central timing mechanism. Time estimation in the absence of tonic motor response yielded a slowly incrementing negative shift, similar to CNV, as shown in Fig. 4. When subjects initiated a hand press voluntarily, but released upon presentation of a tone pip (condition HS), no consistent positive or negative shifts were observed (Fig. 4).

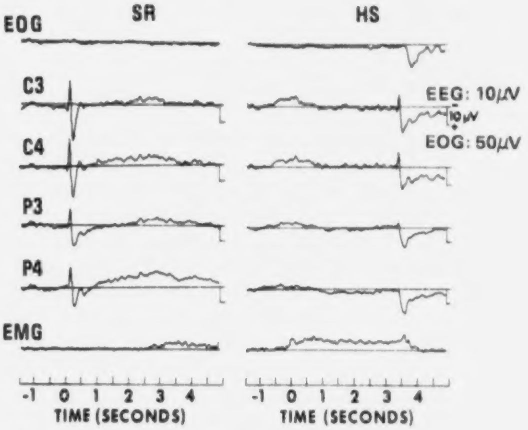

Fig. 4. Summary averages (eight subjects) during time estimation without contraction (SR) and contraction without time estimation (HS). Negative shifts were observed during SR, but no consistent shifts were found during HS.

Discussion

Results of this experiment confirm our previous report (Otto et al. 1977) of a prolonged positive potential over the centroparietal region of the brain during tonic motor activity. Similar motor-related positive shifts have been noted previously (Gilden et al. 1966, Jones and Beck 1975), but never studied systematically.

Other investigators report conflicting evidence. Vaughan et al. (1970) observed a prolonged negative shift in epidural recordings over the contralateral motor cortex of monkeys during sustained wrist contractions. Rebert et al. (1976) also observed sustained negative shifts at the vertex in humans during tonic weight pulling. Rebert's experimental design was confounded, however, by external stimuli and a secondary reaction-time task which bracketed the weight-pulling within an extended CNV interval.

Otto et al. (1977) have shown that negative anticipatory and positive response-related processes sum linearly on the scalp when tonic motor activity is superimposed on a CNV-eliciting interval. Since the negative potential tends to be larger than the positive potential in this situation, the observed effect of sustained key-pressing is a reduction in CNV amplitude. Papakostopoulos and Cooper (this volume) have confirmed this phenomenon.

Further evidence of the interaction on the scalp of negative and positive slow potentials occurs in this study. When subjects were asked to briefly squeeze the dynamometer 3 sec after presentation of a tone pip (time estimation without tonic contraction), a slow negative shift was observed consistent with McAdam's (1966) report.When subjects were instructed to initiate and maintain contraction until presentation of the tone pip, however, no consistent positive or negative slow potentials were observed. The simplest explanation of this finding is that negative anticipatory and positive response-related potentials summed to zero at the scalp recording sites.

Is the slow positive shift during motor response an extracerebral artifact? All trials containing significant eye movements as indicated in EOG tracings were carefully excluded from averages. Picton and Hillyard (1972) and Corby et al. (1974) have described a cephalic skin potential artifact which could conceivably contribute to the observed waveforms. This artifact was not observed, however, by Picton or Corby when linked ear references were used, as in the present study. The small amplitude of positive shifts (5 to 10 μV) also is inconsistent with a cephalic skin potential.

Another possibility is that the baseline is biased in a negative direction by the readiness potential that precedes movement. The baseline measure was computed from the initial 400 msec of data in each average. The baseline epoch terminated 2.3 sec prior to the EMG trigger and appeared to precede the onset of the readiness potential in most cases. The precise onset of the readiness potential, is, however, difficult to determine since it is an internally generated event not necessarily time-locked to the initiation of movement.

A closely related problem concerns the selection of an appropriate trigger event. EMG onset of the brachioradialis muscle was chosen since this large superficial muscle discharges prominently and reliably during fist clenching. Many other muscles of the forearm also participate in this complex motor response. A transducer attached to the handle of the dynamometer might have provided a more reliable trigger index of movement onset.

The question of the functional significance of the prolonged positive shift remains unanswered. Results of the delayed response-time estimation task argue against the central timing hypothesis. If the positivity reflects afferent input from peripheral muscles, one would expect the amplitude to increase directly with the force of pressing. One would also expect the waveform to be larger over the somatosensory region contralateral to response. The fact that neither effect was observed casts doubt on the peripheral afference hypothesis.

Considerable evidence reviewed by Hazemann (this section) indicates that afferent input is inhibited during movement. Marczynski (this volume) concludes from an extensive review of behavioral, electrophysiological, and pharmacological data that slow surface-positive brain potentials, including the P300, RCPV, and other motor-related positivities, reflect corticofugal suppression (inhibitory modulation) of the ARAS. Papakostopoulos and Cooper (this section) propose a similar explanation of the CNV reduction observed during the Jendrassik maneuver. Slow positive shifts described in this study are presumably related, functionally and neurophysiologically, to these other ERP phenomena. Further research is needed to evaluate the corticofugal inhibitory hypothesis of Marcyznski and Papakostopoulos, and to clarify the relationship of the expanding family of slow positive ERPs.

Summary

A prolonged positive shift was observed at central and postcentral recording sites during tonic contraction of the hand. No consistent hemispheric differences or linear relationship with the force of contraction were found. It appears unlikely, therefore, that this waveform reflects proprioceptive or kinesthetic feedback from responding muscles. CNV-like negativity during simple time estimation suggests, furthermore, that the positive waveform does not reflect a central timing mechanism.

Acknowledgment

The authors thank J. H. Knelson for support and L. Ryan and J. Bedrick for technical assistance.

ELECTRICAL ACTIVITY OF THE BRAIN ASSOCIATED WITH SKILLED PERFORMANCE

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Self-paced and externally triggered movements are preceded by sustained negative brain potential changes known respectively as Bereitschaftspotential (BP) (Deecke et al. 1969) and contingent negative variation (CNV) (Walter et al. 1964). The movements employed are usually simple brisk flexions or extensions of a finger with no other demand imposed on the subject. In the case of the CNV, reaction time to the imperative signal is usually measured and a controversial literature has developed (McCallum and Knott 1973, Papakostopoulos and Fenelon 1975). When studied in isolation, reaction time, limb displacement, or development of muscular force, however important they may be for movement, contribute little to our understanding of the organization and development of skillful action. An experimental paradigm was devised in which brain activity was recorded during a manipulative task demanding precision and improvement of performance by providing the subject with real-time information on the outcome of his action. Comparison was made with more conventional situations where only a brisk motor action was required.

Method

Seven subjects, aged 18 to 34 and including five male and two female, were investigated. Four were left-handed and three were right-handed.

The subject sat in a comfortable chair facing the 10-cm screen of a cathode ray oscilloscope (CRO). In each hand, he held a plastic ball 3 cm in diameter fitted with a button that could be pressed. The excursion of the button was 5mm. Pressing with the left thumb initiated a single sweep of the oscilloscope spot; pressing with the right thumb stopped the sweep. The spot velocity was 1 m/sec. The subject was told to initiate the sweep using the left hand and stop it with the right within ±1 cm of the center of the CRO screen, i.e., within a 40- to 60-msec interval following sweep initiation. The above procedure will be referred to as the skilled performance test (SPT). A PDP-12 computer was programmed to acquire EEG and EMG data for 1.2 secs preceding and 0.8 secs after the initiation of the trace. The sampling rate was 250 points/sec. The latency between left and right-hand press was also computed.

For each trial, six EEG and three EMG channels were recorded and stored on digital magnetic tape. EEG electrodes were placed at Fpz, Cz, and 5 cm lateral to the midline 2 cm anterior (precentral) and 2 cm posterior (postcentral) to the central sulcus of both hemispheres. EMG was recorded from left forearm flexors and extensors and right forearm flexors. The time constant and high-frequency response (-3 dB) were 5 sec and 70 Hz for EEG and 0.03 sec and 3000 Hz for EMG.

The experimental procedure included 24 trials with left-hand press (LHP), 24 trials with right-hand press (RHP), 24 trials with both-hand press (BHP), and 100 trials of the skilled performance test, all self-paced.

Stored data were analysed either as single trials or averages. Averaging was done with two different criteria according to the temporal order or precision of responses. In order to examine temporal effects, three averages of 24 trials of LHP, RHP, and BHP conditions and four averages of 24 successive trials of SPT were computed. To classify data in terms of performance, the time following initiation of the spot by the left-hand press was separated into successive 20-msec intervals. Correct performance was defined as right-hand press in the interval between 40 and 59 msec. Trials in which the right-hand press was early (20 to 39 msec) were called -wrong (-W) and late (60 to 79 msec) were called +wrong (+W).

Mean amplitude measurements were computed for three different 200-msec epochs for individual trials and averages as follows: (1) immediately preceding left EMG onset-termed Bereitschaftspotential (BP), (2) immediately following left EMG onset-termed motor cortex potential (MCP) as suggested by Papakostopoulos et al. (1975), and (3) commencing 350 msec after left EMG onset. The baseline for measurements was the mean amplitude of the initial 200 msec of data. The Wilcoxon matched-pairs signed-ranks test and the paired t-test were used to evaluate findings.

Results

Subjects averaged 42.4 correct trials (range: 23-57). The 700 total skilled performance trials included 155 early (-W), 297 correct, and 131 late (+W) trials; 117 trials occurred outside these intervals. The longest latency to right-hand press was 150 msec. Early presses significantly decreased (N=7, t=5, p < .05) while late presses significantly decreased (n=7, t=0, p=.02) in the latter part of the experiment. The frequency of correct presses increased slightly, but not significantly, across trials.

Measurements of brain potentials, eye artifact (Fpz) and EMG averaged across subjects for each experimental condition are shown in Table 1. Note that vertex BP and MCP measures for LHP, RHP, and BHP conditions were very similar, although lateral measurements were differentially affected by the responding hand. For all four lateral electrodes for all subjects combined, the difference between the measures using the contralateral hand and those using the ipsilateral hand was significant both for the BP (n=14, t=4.64, p < .001) and for the MCP (n=14, t=4.85, p < .001). This result suggests lateralization of both the BP and MCP components. Table 1 also indicates different antero-posterior distributions of these components. BP was maximal at central and postcentral locations, while the MCP was maximal precentrally. Values of the third measure were small and inconsistent at all recording sites in conditions LHP, RHP, and BHP. Typical waveforms from one subject are shown in Fig. 1A.

Engagement in the skilled performance test produced marked increases in the amplitude of BP and MCP components and the emergence of a large, slow positive component peaking about 400 msec after left EMG onset. This positive component was maximal at the vertex and averaged 14.2 μV (range: 4.5 to 21 μV) across subjects. Since this large positive component appeared only during the SPT, it was called *skilled performance positivity* (SPP). This waveform is illustrated for one subject in Fig. 1B.

In order to assess the electrophysiological effects of performance, BP, MCP and SPP measurements were pooled across all electrode sites to derive the mean voltage of correct and wrong (±W combined) trials for each subject. BP (n=7, t=2.55, p < .05) and MCP (n=7, t=2.2, p < .1) measures were greater for correct than wrong trials. SPP and EMG amplitude did not vary consistently as a function of correct/wrong response (Fig. 2).

No significant temporal order effect was observed in any electrophysiological measure.

Discussion

EEG, EMG, and behavioral data were collected during two types (skilled and unskilled) of self-paced motor activities. Unskilled actions consisted of initiating the sweep of an oscilloscope beam with either or both hands. The outcome of this action was invariant. Skilled actions entailed the initiation and termination of the sweep within very narrow limits (40 to 60 msec), a paradigm that permits the study of movement-related brain macropotentials (MRBMs) during skilled manipulative performance.

Considerable changes were observed in MRBM patterns when self-paced movements were directed toward a specific objective as opposed to stereotyped movements without any apparent purpose. Both the Bereitschaftspotential (BP) and motor cortex potential (MCP) were larger in amplitude during skilled compared to unskilled performance. The major finding, however was the emergence during skilled actions of a broad positive component that peaked about 400 msec after EMG onset. This component was observed only in the skilled task and, therefore, has been termed skilled performance positivity (SPP).

Since scalp data reflect a spatial average of underlying brain activity (Cooper et al. 1965), the increase in BP amplitude during skilled performance could reflect either increased cortical synchronization or increased cortical negativity. The significance of this finding is not clear, although the BP ratio of skilled/unskilled tasks could conceivably provide a useful electrophysiological index of brain efficiency.

Kutas and Donchin (1974) have shown that BP varies as a function of contractile force. BP differences observed in this study cannot be attributed simply to the force applied in the two tasks because significant differences in BP amplitude were observed when correct and wrong trials were selectively averaged. Rectified EMGs were the same for both sets of trials.

The MCP has been interpreted elsewhere (Papakostopoulos et al. 1975) as an index of peripheral

Table 1. Mean Voltage (and S.D.) in μV of Bereitschaftspotential (BP), Motor Cortex Potential (MCP), and Skilled Performance Positivity (SPP) During Self-paced Tasks

	Left-Hand Press			Right-Hand Press		
Electrode	BP	MCP	SPP	BP	MCP	SPP
Fpz	+0.4(3.7)	+0.4(2.7)	+2.1(6.5)	+0.0(3.0)	+0.0(2.6)	+0.6(2.8)
Cz	- 3.1(0.9)	- 6.0(2.4)	+1.3(2.0)	- 3.4(4.0)	- 6.3(4.1)	+3.0(3.7)
Prec L	- 1.0(1.3)	- 3.7(2.2)	+1.1(2.5)	- 3.9(2.8)	- 7.3(3.4)	+0.4(3.0)
Prec R	- 3.4(1.9)	- 6.9(1.6)	+0.6(2.7)	- 2.9(2.5)	- 4.3(2.5)	+ 1.4(3.1)
Postc L	- 2.1(1.2)	- 3.6(2.0)	+1.3(1.9)	- 5.0(3.5)	- 6.7(3.4)	+0.6(3.5)
Postc R	- 3.9(0.9)	- 5.9(2.5)	+0.4(2.5)	- 3.1(2.3)	- 3.3(2.2)	+ 2.1(3.5)
EMG FL	+2.8(3.6)	+26.4(21.2)	+1.2(2.0)	0	0	0
EMG FR	0	0	0	+3.6(6.0)	+41.6(20.8)	+1.2(2.8)
	Both-Hands Press			**Skilled Performance Test**		
Fpz	+3.0(2.8)	+3.5(4.2)	+0.2(8.6)	+1.4(3.2)	+0.5(4.2)	+3.7(3.6)
Cz	- 3.0(4.1)	- 7.2(3.9)	+2.5(2.5)	- 10.2(4.7)	- 14.9(5.6)	+14.2(6.0)
Prec L	- 2.0(3.6)	- 6.0(4.8)	+0.2(2.6)	-6.9(4.0)	- 12.7(5.7)	+10.9(4.0)
Prec R	- 3.2(3.5)	- 8.0(2.2)	0.0(3.0)	-8.9(3.2)	- 15.2(4.1)	+9.7(4.9)
Postc L	- 4.7(2.6)	- 8.0(3.7)	- 2.0(3.4)	-8.8(3.7)	- 13.1(5.0)	+10.4(4.5)
Postc R	- 4.7(2.6)	- 7.5(2.5)	- 0.7(8.5)	-9.7(4.1)	- 13.6(5.3)	+9.5(5.7)
EMG FL	+6.0(5.2)	+68.8(47.6)	+4.0(5.6)	+3.2(3.6)	+63.2(46.4)	+3.6(2.8)
EMG FR	+4.8(3.6)	+50.8(15.2)	+6.8(11.6)	+2.8(3.6)	+54.6(22.0)	+7.2(9.6)

reafferent activity from skin, joint, and muscle receptors during movement. The change in MCP amplitude observed in this study could reflect an increase in cortical excitation and, therefore, increased responsivity to peripheral input during skilled actions. Such increased excitability has been observed in a CNV task (Papakostopoulos et al. 1970). Alternatively, the MCP increase could reflect relaxed gating (disinhibition) or selective subcortical facilitation of peripheral input (Frigyes et al. 1972; Papakostopoulos et al. 1975; Hazemann, this section) during skilled performance.

The SPP is a new component in the constellation of movement-related macropotentials. It is distinct in waveform, amplitude, and latency from the P2 component that occurs in averages of unskilled presses (Fig. 1). Since there is little apparent difference in EMG patterns for the both-hand press and skilled performance conditions, the SPP cannot be accounted for in terms of increased reafferent activity.

The time course of the SPP suggests that it may coincide with the realization by the subject that his actions succeeded or failed, i.e., when information concerning the consequences of performance is being processed. Although the task was self-paced, instantaneous visual feedback was available from the oscilloscope to evaluate performance. It is likely, therefore, that the SPP is related to the P300 wave, which has been associated with similar concepts of information delivery, resolution of uncertainty, and feedback (see Tueting, this volume, for an extensive review of the P300 literature).

Few data are available concerning the neural substrate of the SPP or P300. Marczynski (1972 and this volume) has described similar slow positive shifts in cats associated with the delivery of appetitive reinforcement. Otto et al. (1977 and this section) have described prolonged positive shifts associated with sustained motor responses. The association and

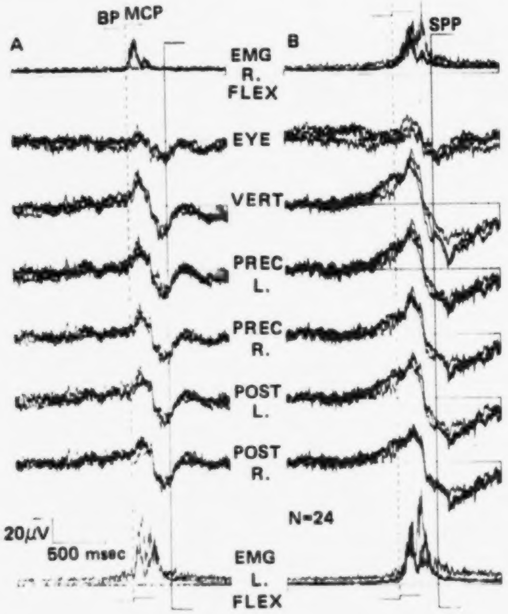

Fig. 1. A. Superimposed averages of brain and EMG potentials during left-, right-, and both-hand presses of a button. B. Data from the same subject and locations during the skilled performance test. Horizontal bars indicate measurement epochs.

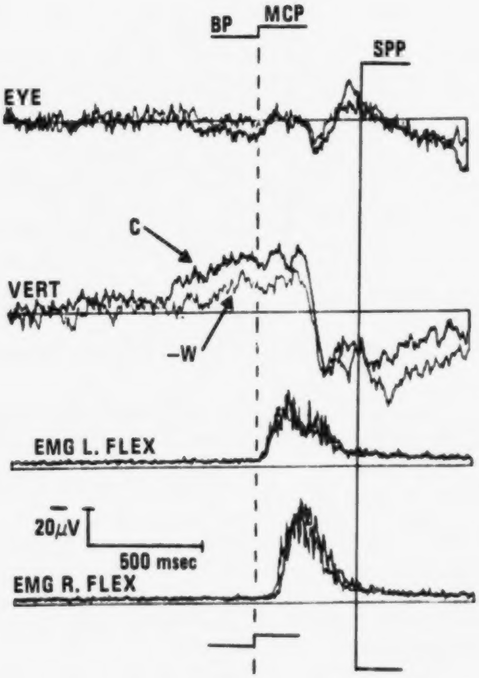

Fig. 2. Comparison between wrong (-W) and correct (C) trials during the skilled performance test. Horizontal bars as in Fig. 1.

significance of these various movement- and reinforcement-related slow positive macropotentials remain to be elaborated in future studies.

Summary

Movement-related brain macropotentials (MRBMs) were compared during skilled and unskilled self-paced motor tasks. Engagement in a task that required precisely coordinated movements of both hands yielded increased amplitude of the BP and MCP and the emergence of a new component called skilled performance positivity (SPP). The BP, MCP, and SPP can be differentiated in terms of topographical distribution and functional significance. The BP seems to be related to the organization of preprogrammed action, the MCP to movement-generated reafference, and the SPP to the evaluation of performance outcome.

Acknowledgments

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THE ELECTROMYOGRAM, H REFLEX, AUTONOMIC FUNCTION, AND CORTICAL POTENTIAL CHANGES DURING THE JENDRASSIK MANEUVER

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During the foreperiod of a simple reaction time (RT) experiment, when sustained potentials known as the contingent negative variation (CNV) develop (Walter et al. 1964), the excitability of the spinal monosynaptic reflex increases (Papakostopoulos and Cooper 1973, 1976). However, the relationship between the development of cortical sustained negativities and increase in the excitability of the spinal monosynaptic reflexes, as measured by the H reflex technique (Paillard 1955), is not a simple one as the two phenomena show a different time course. It has been proposed, therefore, that these two phenomena, and heart rate deceleration which accompanies them, are not causally related but are mediated through a common mechanism in the brain stem that integrates the whole body reaction to the stimulus and response situation (Papakostopoulos and Cooper 1973). To test this hypothesis further, we decided to study the time course of H reflex excitability and CNV development in two situations with similar stimulus conditions, but different response requirements. The first situation was the simple RT experiment (situation 1), the second was the Jendrassik maneuver (situation 2).

This maneuver is a classical clinical procedure designed to increase spinal monosynaptic reflexes. It involves clenching the fist to an external command and relaxing it to another. By replacing the verbal commands with two stimuli, 2 sec apart, and appropriate instructions to press a button to the first stimulus and release it to the second, the situation is similar to a simple RT experiment (situation 1) with the addition of initiation and sustainment of a continuous motor output during the foreperiod.

Previous data by Donchin et al. (1973), McCallum and Papakostopoulos (1972), and Otto et al. (1973a, 1977) where motor action has been sustained during the foreperiod, suggest that the CNV during such a procedure should be smaller in comparison with the CNV to similar external cues in the simple RT experiment.

Method

Five female and four male volunteers (mean age, 24 years) were paid to participate in the study. Monosynaptic reflexes (H reflex) were electrically elicited at various times during and after the 2-sec foreperiod of a simple RT experiment with a click as S1 and a tone as S2 and an average intertrial interval of 29 ± 11 sec. The H reflex was elicited once per trial in pseudorandom order 0.2, 1, 1.5, 1.8, 1.9 sec after S1 and 0.2, 0.5, 2, 5, 10 sec after S2 by a 0.5-msec electrical pulse applied to the tibial nerve in the popliteal fossa.

Five sequences each of 10 trials were presented in which the subject responded to S2 by pressing a button with his left thumb (task 1) and five sequences in which he responded to S1 by a press that had to be maintained until release after the presentation of S2 (task 2). Either of these actions to S2 caused the cessation of the tone. The occurrence of stimuli for eliciting the CNV and H reflex was controlled by the PDP-12 computer which was also sampling and displaying data. RT was measured and printed out on-line. Before initiating the trigger pulse for each trial, the computer measured and stored the R to R interval for 5 heart beats. The fifth beat initiated the stimulus sequence and S1 appeared 1 sec later. This procedure was used to establish EEG, EMG, and heart rate baseline before S1. EMG of forearm flexors, gastrocnemius, and tibial anterior muscles from surface electrodes were each sampled at 1-msec intervals until 1 sec after S2. Respiration (chest expansion) and heart beat intervals continued to be stored for 6 and 10 sec after S2, respectively. Electrodermal resistance (EDR) was also monitored.

For the H reflex, the total sampling time was 50 msec. The CNV, examined during a 4-sec epoch, was recorded from the vertex, C3, and C4 referred to linked mastoid process. A nasion + 2-cm electrode referred to the same reference was used to monitor eye movements and also served for compensation of the vertex channel. A modified 16-channel Elema-Schonander electroencephalograph acted as the main amplification system. For EEG, respiration, and EDR, a time constant of 5 sec was used. Special Ag/AgCl electrodes, selected to have less than 1-mV potential between any pair in distilled water, were used. Separate amplifiers with 10-Hz bandwidth were used for recording the H reflex. Individual trial data were stored for further off-line analysis.

Results

RTs to S2 in tasks 1 and 2 were very similar (267 ± 60 msec and 255 ± 54 msec, respectively). RTs to S1 in task 2 were consistently slower (391 ± 91 msec) than those to S2 in both situations.

EMG activity from the forearm muscles in task 1 was absent or just detectable during the S1-S2 period. After S2 the phasic EMG activity leading to the action of pressing was recorded (Fig. 1 left). The EMG in situation 2 was characterized by an initial phasic increase followed by a diminished and sustained activity until after S2, when a new phasic increase appeared (Fig. 1 right). The latency of the phasic EMG increase after S2 in both situations was similar. This latency was always shorter than the latency of the phasic EMG increase following S1 in task 2. No EMG activity was recorded from leg muscles at any stage of task 1 or 2. The consistent appearance of phasic EMG activity after S2 in task 2 suggests that the button release was an active manipulative action that involved flexor and extensor forearm muscle groups. In other words, the button release was not a passive concomitant of the cessation of action by the forearm flexors.

CNV from the vertex and two central areas for all subjects tested was always smaller during the press-wait-release situation (task 2) compared with task 1. This is illustrated in Fig. 2 where the grand averages obtained from all subjects for each condition at the vertex and central areas are shown. The possibility of differences due to eye movements can be excluded as the activity at Fpz during the interstimulus period was very similar for the two situations.

The H reflex elicited during the S1-S2 period was larger than H reflexes elicited 2 to 10 sec after S2 for both situations. This increase during the foreperiod was larger in task 2 than in task 1. This is shown for the whole group in Fig. 2 and for one subject in Fig. 3. A further increase of the H reflex was recorded 200 msec after S2 in both situations and 200 msec after S1 in task 2. This additional increase coincided in time with the phasic EMG increase leading to press or release after S2 and to press after S1 in task 2 (Fig. 2). No consistent changes in electrodermal potentials were recorded in the two situations.

The heart rate during the foreperiod of task 1 decreased in all subjects; this decrease was not observed in task 2. The deceleration during the foreperiod in task 1 and the absence of it in task 2 for all subjects tested is graphically represented in Fig. 2.

Discussion

Data from task 1 confirmed previous findings (Papakostopoulos and Cooper 1973, 1976) that increased excitability of spinal monosynaptic reflexes and heart rate deceleration accompany CNV development during the foreperiod of a simple RT experiment. A very different pattern emerges in task 2, where a further increase of H reflex excitability occurs in association with diminished CNV and no heart rate deceleration. RT to the second stimulus is similar in both tasks.

The EMG and H reflex data provide clues concerning the possible mechanism and significance of the neurophysiological difference observed between the two tasks. Two basic types of motor action were involved in these tasks, *phasic* pressing or releasing in responses to stimuli, and *tonic* pressing during the interstimulus interval of task 2. Of all the variables measured, only the H reflex from the leg extensor muscles paralleled the EMG changes in forearm flexors. That is, phasic increases in H reflex excitability were observed with each phasic action of forearm muscles, while a tonic increase in monosynaptic excitability occurred with sustained pressing.

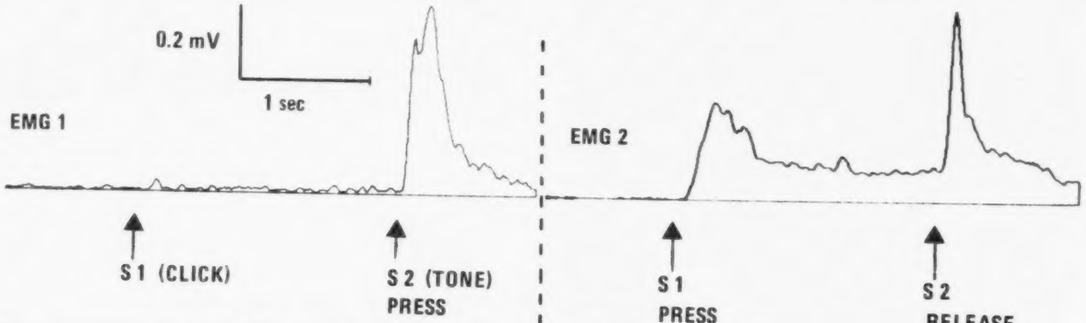

Fig. 1. Averaged rectified EMG from the forearm flexors in task 1 (left) and task 2 (right) from one subject.

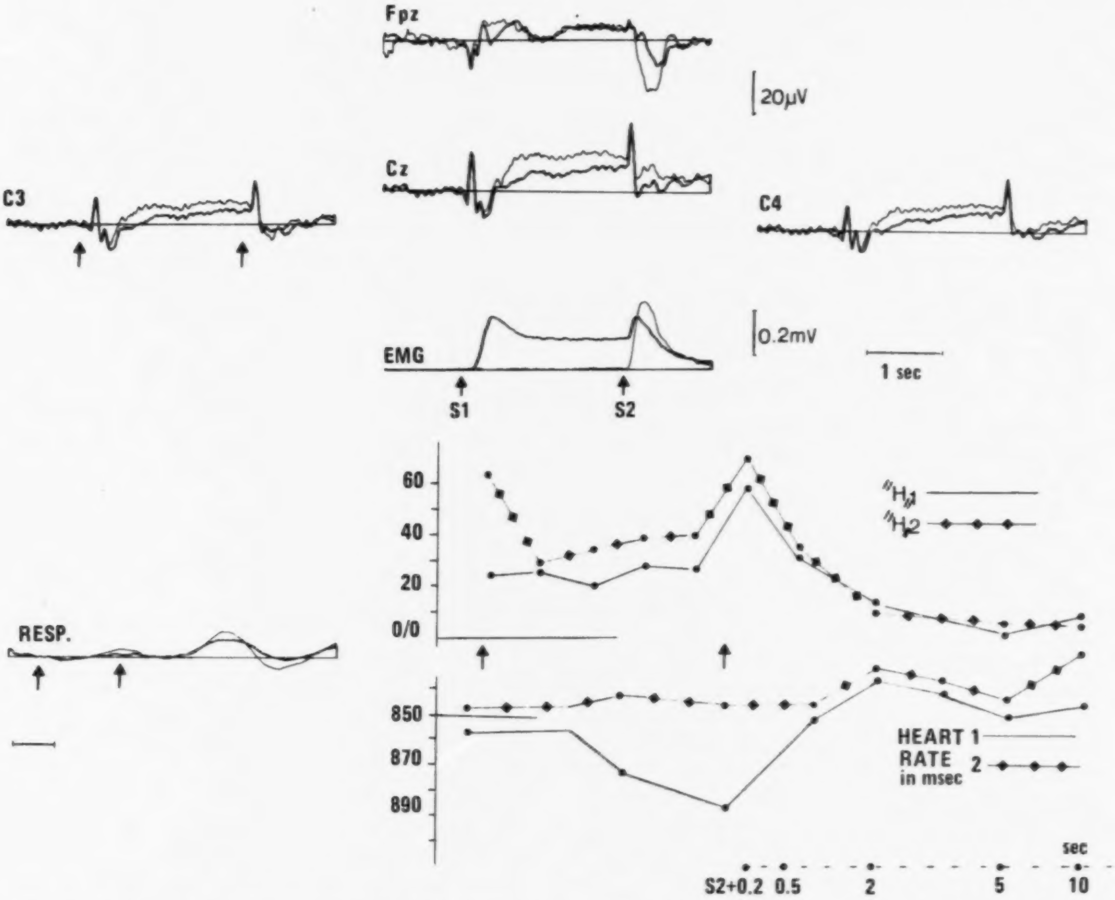

Fig. 2. Grand averages (nine subjects) of the CNV, rectified EMG of the left forearm flexors (EMG), respiration (RESP), H reflex (H1, H2), and heart rate changes. The CNV, EMG, and RESP of task 1 are shown as thin traces, those of task 2 as thick traces. The H reflex (upper graphs) and heart rate (lower graphs) of task 1 are shown as continuous lines and these of task 2 as lines with squares. Measures were obtained at points indicated by dots. Time calibration in RESP, 1 sec. Arrows indicate the time of S1 and S2 presentation. Time after S2 is nonlinear for H reflex and heart rate.

Gottlieb et al. (1970) and Pierrot-Deseilligny et al. (1971) attribute phasic increases in H reflex excitability during arm flexion to involvement of the corticospinal or pyramidal system. Phasic actions in this study were presumably mediated by pyramidal pathways. Other observed cortical and autonomic changes may also relate to pyramidal function. The CNV decrease associated with sustained pressing, for example, could result from direct corticofugal action on brainstem structures. It is conceivable that the corticobulbar component of the pyramidal system selectively excites descending tracts of the reticulospinal system and simultaneously inhibits ascending reticular pathways. Selective inhibition and facilitation of subcortical pathways by corticofugal action have been demonstrated in animals (Frigyesi et al. 1972; Skinner, this volume) and probably in man (Papakostopoulos et al. 1975). Moreover Steriade (1969) has shown that reactivation of motor-sensory (precentral) cortex, in contrast to other cortical regions, diminishes with reticular activation. Diminished cortical activation, therefore, is not necessarily inconsistent with increased motor output.

If this is the case, CNV reduction in task 2 should be selective for motor sensory areas. Otto et al. (1973b, 1977) have shown, however, that sustained motor activity during the S1-S2 interval yields a generalized decrease in CNV over anterior (Fz) and posterior (Pz) areas, as well as central regions.

Dimished CNV could be attributed alternatively to reafferent feedback from peripheral receptors that discharge during tonic motor activity (cf. Matthews 1972). Several strands of evidence are inconsistent with this hypothesis. McCallum and Papakostopoulos

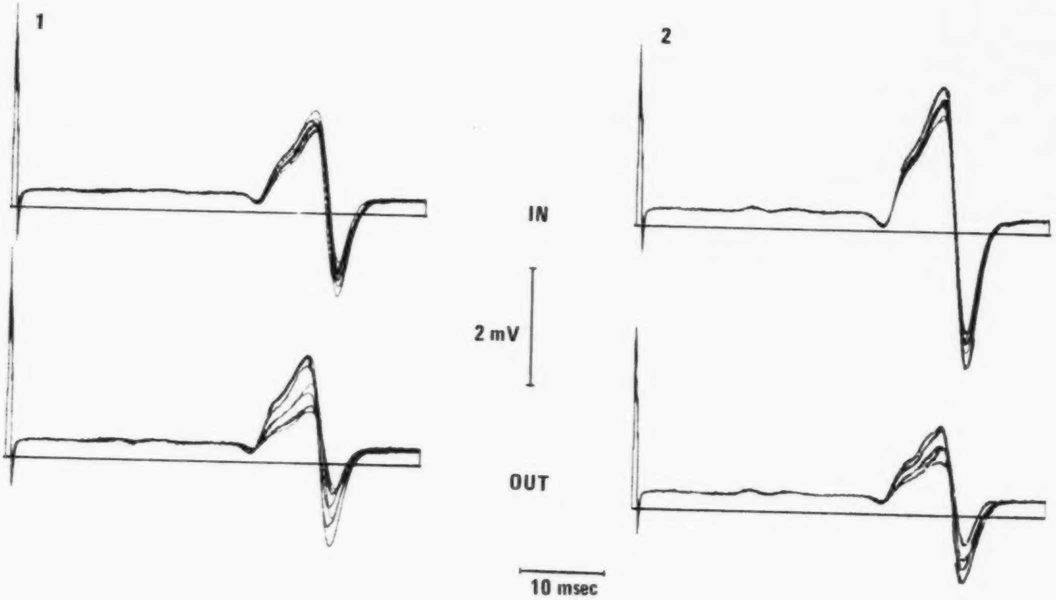

Fig. 3. Superimposed single H reflexes in task 1 (left) and task 2 (right) elicited 5 and 10 sec after S2 (lower traces–Out) and during the period when the CNV develops (upper traces–In). Note that H reflexes during CNV (upper traces) are larger than those elicited out of the CNV period. Yet this H increase is consistently larger for task 2 (upper right) than for task 1 (upper left).

(1972) have shown that CNV amplitude is not affected if the button is depressed continuously and released momentarily in response to S2. This finding suggests that the initiation of action at the beginning of the interval, rather than sustained response, is the critical factor. This initiation should be followed by feedback from phasic receptors in the periphery. If such feedback can be seen with scalp electrodes, it should appear as short duration negativity (Wilke and Lansing 1973; Jones and Beck 1975; Papakostopoulos et al. 1975; Papakostopoulos, this volume). One might expect such negativity to summate with the CNV and appear as an increase of the sustained potential. The results of this experiment are clearly contrary to this argument. Two other papers in this section (Hazemann et al., Otto and Benignus) also present evidence inconsistent with the reafference hypothesis.

Another approach is to assume that the reduction in CNV during tonic motor activity is phenomenal rather than real. For instance, if another positive potential occurred during the foreperiod in parallel with the CNV, the true CNV amplitude might be masked. The existence of a prolonged positive shift during sustained contractions has, in fact, been demonstrated by Otto et al. (1977 and this section). Prolonged positivity following skilled performance has also been described (Papakostopoulos, this section). Otto et al. (1977) showed, moreover, that the decrease in CNV amplitude when sustained motor activity was superimposed could be accounted for by the simple linear combination of anticipatory negative and response-related positive components.

The neuronal generators and functional significance of such positivities are as yet unknown. If these potentials are related to the reinforcement contingent positive variation (RCPV) reported by Marczynski (1972), increased rhythmicity of the sensorimotor areas during task 2 could be expected. This possibility seems remote in terms of present data, which suggest that motor activity, phasic or tonic, is accompanied by suppression of sensorimotor rhythms (Chatrian 1959; Papakostopoulos, this volume).

Summary

During the 2-sec interval between a warning stimulus S1 and a second stimulus S2 that requires a motor action by the subject, the brain develops sustained potential changes, known as the contingent negative variation (CNV), the H reflex increases in amplitude, and heart rate decreases. During the same period, EMG of relevant muscles is silent or only moderately active. To assess the significance of myographic activity during the S1-S2 period, nine subjects pressed a switch with the left thumb when S1 occurred and released it at S2.

In both situations, the reaction times for releasing or pressing the switch to S2 were similar. However, the CNV was significantly smaller and the heart rate

deceleration during the S1-S2 interval did not occur when motor action was required during this interval. At the same time, there was a significant increase of the H reflex amplitude beyond that normally seen in the simple S1-S2 preparatory situation. A dissociation has thus been demonstrated between cortical and spinal excitability extending to autonomic function and behavioral output. The effect of the motor action on subcortical centres that underlie cortical negativity can be seen as a result either of reafferent activities generated by the action itself or, most probably, as a direct inhibition by cortical efferents.

OCULOMOTOR COMPONENTS OF EVENT-RELATED ELECTROCORTICAL POTENTIAL IN MONKEYS.

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This report concerns the extent to which event-related cortical macropotentials, particularly those time-locked to sensory stimuli, reflect oculomotor processes. Cortical structures have long been implicated in oculomotor functions as a consequence of the findings of electrocortical stimulation and single unit recording studies. Stimulation of the frontal and occipital eye fields in the monkey (Brodmann's area 8, 18, and 19) result in eye deviations generally contralateral to the hemisphere stimulated (Crosby et al. 1952, Ferrier 1875, Wagman 1964). Moreover, brief pulse stimulation of the awake monkey's frontal eye field (FEF) elicits single saccades of specific amplitude and direction with latencies of 15 to 25 msec (Robinson and Fuchs 1969). The latter finding strongly suggests that the FEF serves an oculomotor command function. This view is challenged, however, by reports indicating that the vast majority of FEF cells, which indeed discharge in relation to saccadic and pursuit eye movements, fire during, or following, the movements, but never before them (Bizzi 1968, Bizzi and Schiller 1970, Mohler et al. 1973).

Despite the evidence of cortical involvement in the control of eye movements, event-related cortical macropotentials have rarely been examined in relation to the oculomotor processes they may reflect. This has been due in part to the difficulty in dissociating between potentials of cortical origin related to eye movements and those artifactually generated potentials arising as a consequence of the rotation of the corneofundal dipole with eye movements (Hillyard and Galambos 1970, Peters 1967). Furthermore, in animal studies in which eye movement artifacts can be reduced by means of bipolar recording electrodes placed directly on the cortex equidistant from the eyes and use of differential amplifiers affording common mode rejection of eye potentials, great difficulty is encountered in the behavioral control of eye fixations and the elicitation of eye movements of specifiable amplitude and direction. The present report presents the results of investigations in which many of these difficulties have geen successfully overcome. Our findings indicate that significant components of prefrontal electrocortical potentials evoked by visual stimuli upon which a monkey must fixate reflect cortical mechanisms of oculomotor control that both precede and follow accompanying saccadic eye movements.

Methods

Subjects

Nonpolarizable Ag/AgCl electrodes were chronically implanted in prefrontal (bilateral), precentral, and occipital cortex and also subcutaneously across the eyes for horizontal electrooculogram (EOG) recording in two stumptail monkeys. Cortical electrodes were implanted in pairs with one electrode of each pair on the pial surface and the other in subjacent white matter (5- to 10-mm tip separation). The prefrontal surface electrode was located on cortex within the posterior half of the principal sulcus, and the depth reference was in white matter of the lateral bank of the sulcus. EOG electrodes, of the type described by Bond and Ho (1970), were cemented to the nasal and temporal sides of the bony orbit. All electrode leads were soldered to the Amphenol connectors, which were then fixed to the skull with stainless steel screws and dental cement. Embedded in the resulting cement cap were two parallel brass tubes (oriented perpendicular to the saggital plane) for head immobilization in the testing apparatus.

Apparatus

During testing, the monkey was seated in a restraining chair containing a response lever within easy reach. The lever had a 5-mm stroke, and 120 g force was required to depress it and activate a microswitch. The chair was positioned in an electrically shielded soundproof chamber so that the monkey's head was between two parallel plates rigidly fixed to the chamber. The plates contained slots which permitted attachment of metal rods that were inserted through the tubes in the monkey's skull cap to the plates. Once the monkey's head was immobilized in this manner, the tip of an adjustable brass tube for injection of liquid rewards was brought to the monkey's mouth. For the presentation of visual stimuli, a perimeter containing five light-emitting diodes (LEDs) 20° apart was situated at eye level in front of the monkey at a distance of 1 meter. Onset and duration of LED illumination (equated for intensity and color), as well as the sequence of light presentations, was controlled by an external program panel.

The chamber also contained connectors and low-noise cables for recording EOG and electrocorticogram (ECoG) events. Inputs were led to low-level preamplifiers outside the chamber, and amplified signals were stored on FM magnetic tape for off-line analysis with a PDP-12A computer. A videotape system also permitted simultaneous recording of electrographic and eye movement events.

Procedures

In order to obtain steady fixations and saccadic eye movements of known amplitude and direction, monkeys were trained on a difficult reaction time (RT) task. A single fruit juice reward was delivered if the animal pressed the lever twice, once during the 0.75-sec dimming of a central (0°) fixation light and again during the dimming of a peripheral test light that was illuminated immediately following the first press. Both fixation and test lights were of variable duration (1.5 sec minimum), and the order of test light presentations was random from trial to trial. A DRL schedule was used to eliminate presses during the light-on, but not the dimming, periods. Animals were tested daily until their performance resulted in consistent patterns of lateral eye movements.

In another experiment involving operant conditioning of unilateral cortical slow potential (SP) shift, rewards were made contingent upon on-line computer detection of 3-sec surface-negative SP shifts of 50- to 100- μV amplitude. Conditioned SP events were then correlated with records of eye movements.

Data analysis

During testing, horizontal EOGs and ECoGs from left and right prefrontal, left precentral, and left occipital cortex were recorded with dc amplifiers and the data were stored on FM magnetic tape. Cortical evoked potentials and EOG events resulting from test-light presentations were computer-averaged off-line, with separate averages obtained from each area for each of the five test lights. Each average represented the data from 40 similar stimulus presentations with a time base of 2 sec. Peak-to-peak amplitudes of the evoked cortical potentials and peak latencies were computed. These in turn were related to the amplitude, duration, latency, and direction of averaged lateral eye movements.

Results

Stimulus-triggered eye movements

EOG and videotape recordings made during successful RT task performance by two monkeys (i.e., when 90% or more of the monkey's paired presses were rewarded) indicated that the animal's gaze was directed towards the fixation light when presented and that appropriately directed saccadic eye movements followed test light onset. Computer-averaged EOG activity time-locked to the different test light presentations confirmed the existence of characteristic patterns of eye movements to each of the test lights (Fig. 1). The averaged recordings appear similar to records of individual saccadic movements, with mean latencies of the averaged movements ranging between 240 and 318 msec (Table 1). The amplitude of the averaged saccades (both initial and final) were linearly related to the angular displacement of the visual targets (Fig. 2A).

Potentials evoked by test stimuli

Prefrontal: Components of averaged electrocortical potentials evoked in prefrontal cortex by test light presentations were observed 22 to 750 msec following test light onset. Generally, two negative (N1, N2) and two positive (P1, P2) peaks could be identified in a N1-P1-N2-P2 sequence (Fig. 1). The N1, P1, and N2 components preceded initiation of saccadic eye movements to the test target by 20 to 150 msec. The rise of the P2 component coincided with the saccadic movement, although its peak amplitude was attained some 100 to 150 msec after the initial saccade was completed. Prefrontal components could only be consistently identified in the hemisphere contralateral to the direction of the stimulus-triggered saccade, i.e., right prefrontal EP components were reliably seen with left movements to the 20° and 40° left targets, whereas the left prefrontal components were seen with right movements elicited by the corresponding right targets (Fig. 1). Amplitudes were significantly larger for more peripheral targets (Fig. 2B and 2C).

Precentral: As many as eight peaks could be identified in averages of precentral events time-locked to onset of the test target. Unlike prefrontal components, these could be identified in averages associated with each test light presentation. The amplitude of these components, some of which preceded (N1 and P1) and the remainder which followed saccadic eye movements, did not vary systematically with test lights in different locations. Mean amplitudes of the first four components (N1, P1, N2, and P2) associated with each test light location were not significantly different (Fig. 2D). These results were not surprising in light of

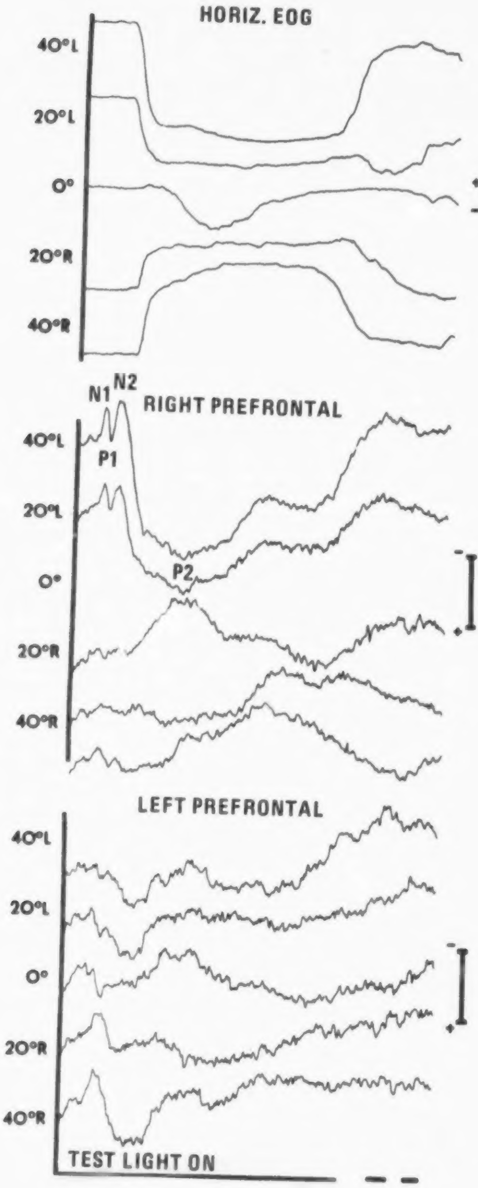

Fig. 1. Averaged horizontal EOG and left and right prefrontal ECoG events time-locked to test light onset. Individual traces represent the average of 40 responses evoked by each test light during a single testing session with Monkey 297. Left (L) and right (R) test lights are indicated to the left of the traces. The time base equals 2048 msec and calibration bars show 100 μV. The minimum test light duration was 1.5 sec, indicated by the horizontal bar at the bottom of the figure.

Table 1. Mean Latencies[a] (msec) of Averaged Saccadic Eye Movements and Prefrontal Evoked-Potential Components for Two Monkeys

Averaged waveform[b]	Test light				
	40°L	20°L	0°	20°R	40°R
Monkey 297					
HEOG	257.6	240.8		285.2	297.2
RFp N1	143.6	144.0			
P1	176.8	177.6			
N2	219.2	221.2			
P2	499.6	509.2			
LFp N1					60.0
P1					103.2
N2					187.1
P2					339.2
Monkey 293					
HEOG	292.4	318.4	293.2	296.0	312.4
RFp N1	85.6	106.8			
P1	161.2	158.4			
N2	221.6	210.4			
P_2	401.2	382.8			
LFp P1					22.4
N1					101.2
P2					316.8
N2					747.6

[a] *Latencies were obtained for only those test lights that produced consistently identifiable waveforms. The mean latencies are comprised of 8 to 15 measures of the time intervals between test light onset and the initial averaged EOG deflection (for saccadic eye movements), and the peak amplitude of each of the averaged EP components.*

[b] *HEOG - horizontal electro-oculogram; RFp - right perfrontal cortex; LFp - left prefrontal cortex.*

the clear implication of precentral areas in the initiation of skeletal motor responses. Since the motor response, namely the lever press, is the same regardless of which test light is presented, no differences in averaged potential would be expected.

Occipital: Evoked-potential components from occipital cortex were observed 40 to 1500 msec after test light onset. The rise of an initial negative component was observed some 40 to 60 msec after target onset, and it attained peak amplitude at about 150 to 200 msec. This was followed by somewhat more variable positive and negative waves with peak latencies of about 300 to 900 msec. The amplitudes of the initial negative wave (N1) and the final positive wave (P2) were greater for the centrally located test targets, i.e., the 0° (fixation) test target and the 20° left and the 20° right test lights (Fig. 2E). However, the differences in the mean amplitudes of these components were not statistically significant.

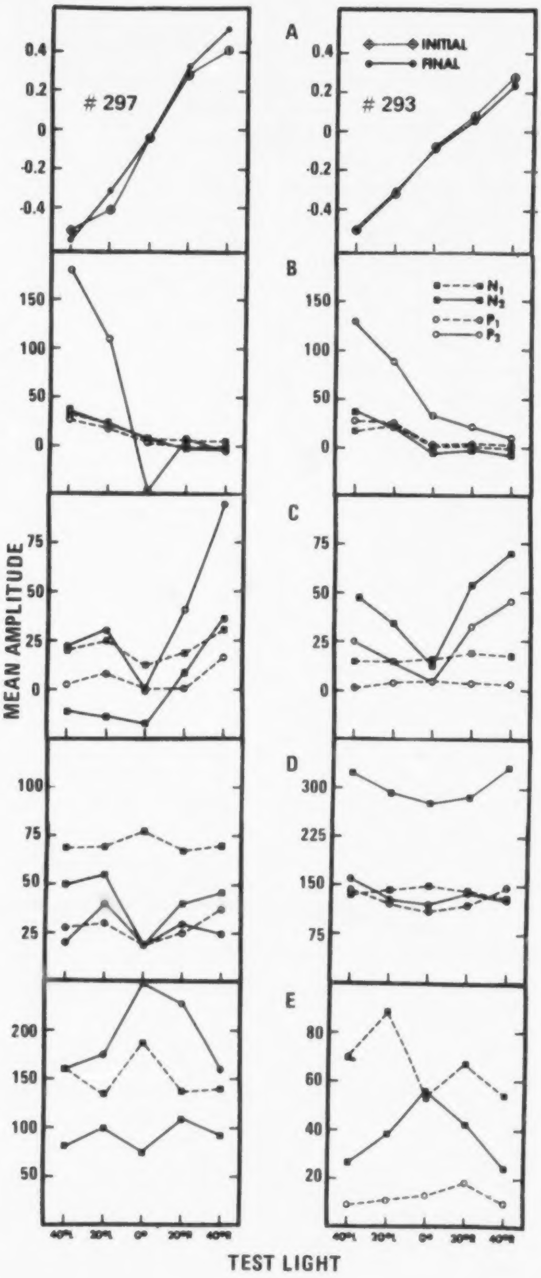

Fig. 2. Mean amplitudes of averaged EOG and ECoG components as functions of test light location. Data for Monkeys 297 and 293 are shown. Amplitude measures are of (A) horizontal EOG, (B) right prefrontal, (C) left prefrontal, (D) left precentral, and (E) left occipital averaged responses. Mean values represent measurements of components seen in eight to fifteen 40-trial averages obtained during consecutive days of testing. Amplitudes are in microvolts except for the EOG, which is in millivolts.

Operantly conditioned slow potential shifts

Reinforcement of unilateral surface negative SP shifts in prefrontal cortex resulted in an increase in the incidence and amplitude of these spontaneously occurring cortical events. Reinforced shifts of 50 to 100 μV amplitude and 2.5 to 3.0 sec duration were accompanied by a series of contralateral saccades and sustained conjugate eye deviations until reward was delivered (Fig. 3). Delivery of reward resulted in rapid centering eye movements, but no marked change in the cortical SP. Contralateral prefrontal SP shifts were completely unrelated to eye movements or reward delivery.

Discussion

This investigation provides clear evidence of electrocortical potentials in prefrontal cortex of monkeys that encode amplitude and direction of stimulus-triggered saccadic eye movements. These potentials are time-locked to the onset of a visual stimulus that the animal is required to fixate upon and appear in the hemisphere contralateral to the direction of the saccade. Moreover, components of these potentials both precede and arise coincidentally with the initiation of horizontal saccades. The duration of the preceding components is less than 100 msec, whereas that of the following components often exceeds several seconds. The recording methods employed do not permit specification with any degree of certainty that the potentials arise from the posterior half of the principal sulcus, or more posteriorly from the traditionally defined FEF (area 8) as a consequence of volume conduction to the recording electrodes in the principal sulcus. However, these potentials are clearly specific to the prefrontal region since averaged recordings of precentral and occipital cortical activity were not consistently related to eye movements. Moreover, it is unlikely that the observed potentials reflect eye movement artifacts. Clearly the issue pertains not to the components preceding the eye movements but to those arising concomitantly with eye movements. The finding that the latter components appear only in the hemisphere contralateral to the direction of the saccade is inconsistent with an eye movement artifact interpretation since saccadic movements involve both eyes and significant potentials of opposite polarity would be expected at homologous locations in the other hemisphere. These were not observed. Furthermore, in the procedure involving operant conditioning of unilateral prefrontal SP shifts, concomitant contralateral saccades were observed during the increase of cortical surface negativity, but subsequent centering eye movements were completely independent of cortical SP shifts, a finding that could not be explained if rotation of the corneofundal dipole was the source of the potentials.

With regard to the functional significance of prefrontal potentials related to eye movements, it would

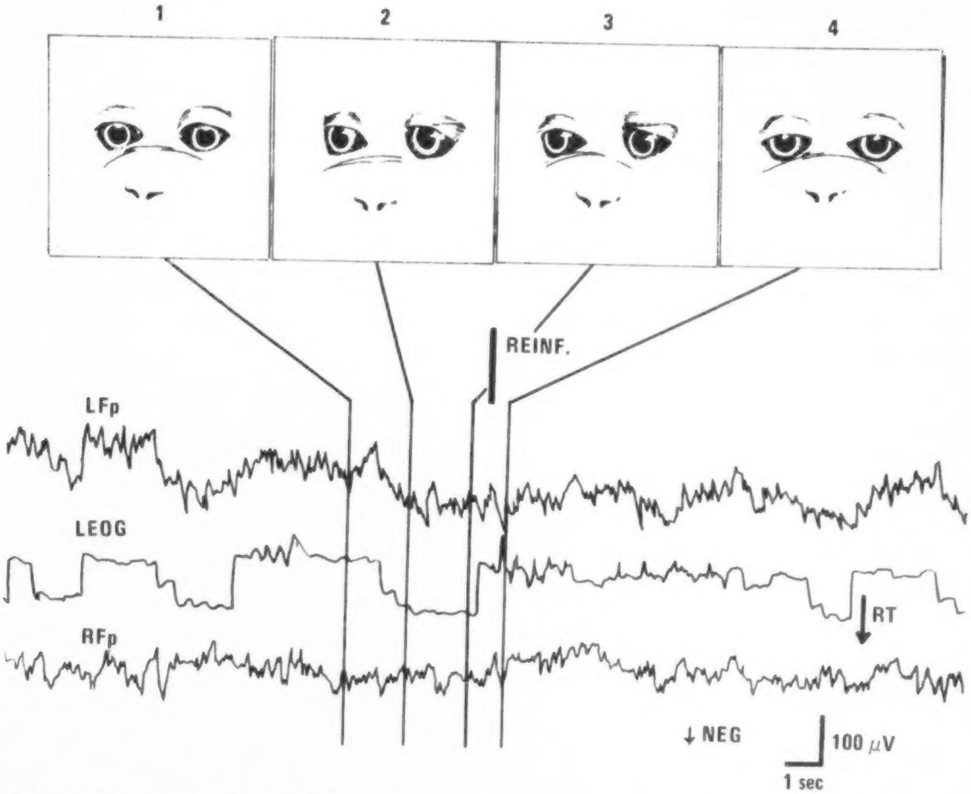

Fig. 3. An operantly conditioned surface-negative cortical steady potential shift in left prefrontal (LFp) cortex and concomitant right (Rt) oculomotor responses indicated in both horizontal EOG and drawings of stop-action videotape recording of eye position. The vertical bar indicates time of food reward. Vertical lines indicate times during bioelectric recordings when eye positions were photographed. Note the lack of response in the homologous right prefrontal (RFp) ECoG recording.

appear that those accompanying and following saccades reflect the sustained activity of FEF neurons, which reportedly discharge during saccades and steady fixations (Bizzi 1968, Mohler et al. 1973). Insofar as the components preceding eye movements are concerned, the finding that the amplitude of these components increases with more peripherally placed visual targets argues against the notion that they simply reflect a visual sensory input to the prefrontal area via known cortical-cortical afferents from areas 18 and 19 (Jones and Powell 1970). Mohler et al. (1973) have reported that FEF cells with visual receptive fields have extremely large fields, and individual cells tend to discharge minimumly, not maximally, when spots of light are presented in the periphery of the field. It is possible, however, that prefrontal potentials preceding saccadic eye movements reflect an enhanced sensory response of FEF neurons that has been observed when the visual target for an impending saccade falls within the receptive fields of a subpopulation of FEF cells (Wurtz and Mohler 1976).

Alternative explanations include the possibility that presaccadic potentials reflect attempted head movements and possible feedback from neck muscles. These views are suggested by the findings of FEF cells that discharge prior to head turning (Bizzi and Schiller 1970) and FEF neurons in the cat that respond, with short latencies, to stimulation of the neck muscles (Dubrovsky and Barbas 1975, Mandl and Guitton 1975). Another possibility is that the observed potentials reflect a corollary discharge mechanism (Teuber 1964) or a motor command system for voluntary saccadic movements, perhaps related to search behavior or attention.

It should be noted that the present data are not the only indication of cortical events preceding eye movements. Lynch et al. (1977) have recently found cells in parietal cortex (area 7) that discharge prior to stimulus-triggered saccades and appear to encode direction of movement, and Schlag et al. (1971) have found cells in the internal medullary lamina of the cat that similarly discharge preceding eye movements. This region is known to receive input from the FEF (Orem and Schlag 1971).

In conclusion, the results of this investigation strongly suggest that significant components of cortical potentials evoked by sensory stimuli can reflect oculomotor processes, particularly if attention to these stimuli by the subject involves saccadic eye movements and eye fixations.

Summary

In order to examine the extent to which potentials evoked in monkeys' dorsolateral prefrontal cortex by visual stimuli reflect oculomotor functions, monkeys with chronically implanted nonpolarizable electrodes in prefrontal, precentral, and occipital cortex, and also subcutaneously across the eyes, were trained on a reaction time task for liquid rewards. The task required that the monkey detect the dimming of a centrally located fixation light and then fixate upon one of five test lights in order to detect its dimming. The test lights were perimetrically presented in random order at 20° and 40° to the left and right of center. Computer averages of cortical potentials time-locked to 40 presentations of each test light, within a daily testing session, revealed prefrontal components that preceded and followed saccadic eye movements. These components were of maximal amplitude for the most peripherally located test stimuli in the contralateral visual field. By contrast, the largest occipital evoked potential components were observed with central stimuli, and precentral potentials showed no variations in amplitude with different test light presentations. The data indicate the evoked potentials in prefrontal cortex elicited by peripherally presented visual stimuli, upon which an animal must fixate, reflect oculomotor processes related to saccadic eye movements.

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III. INFORMATION PROCESSING AND COGNITION

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EVENT-RELATED POTENTIALS, COGNITIVE EVENTS, AND INFORMATION PROCESSING[1]

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This review is based on pre-Conference correspondence among the members of the EPIC IV Information Processing Panel; additional comments from discussion at the conference have also been included. Contributors were: P. Tueting (chairman), New York State Psychiatric Institute, New York, NY; E. Donchin, University of Illinois, Champaign, IL; J. Ford, Stanford University, Palo Alto, CA, D. Friedman, New York State Psychiatric Institute, New York, NY; M.R. Harter, University of North Carolina, Greensboro, NC; S. Hillyard (co-chairman), University of California, San Diego, CA, W. Ritter, Lehman College, Bronx, NY; J. Rohrbaugh, University of California, Los Angeles, CA, W.T. Roth, Stanford University, Palo Alto, CA; D. Ruchkin, University of Maryland, Baltimore, MD, K. Squires, University of Illinois, Champaign, IL, N. Squires, University of Illinois, Champaign, IL, S. Sutton, New York State Psychiatric Institute, New York, NY, and R.T. Wilkinson, Medical Research Council, Cambridge, England.

The papers in this section are divided into two categories: (1) issue-oriented reviews and (2) data papers. The review papers developed out of the correspondence and discussion at the conference and are presented first. Roth considers the issue of how many late positive waves can be defined. Ritter discusses the relationship of ERPs to decision latency, and Ruchkin explains the importance of the concept of equivocation in interpreting ERP data. The relationship of ERPs to orienting is discussed by Friedman. Ford presents template and match/mismatch theory. Sutton and his colleagues document P300 studies relevant to feedback issues. The research reports that follow the review papers relate to one or more of these issues and are representative of current research in the area. Research reports germane to information processing were submitted by R. Cooper, Burden Neurological Institute, Bristol, England; N. Lesevre, Salpetriere Hospital, Paris, France; and J.J. Tecce, Tufts University School of Medicine, Boston, MA, as well as by members of the Information Processing Panel.

Background

New evoked potential (EP) components are emerging so rapidly that it is difficult to determine their validity, let alone their function in information processing. Temporal sequences of components have traditionally been evaluated within a "stages of information processing" framework. However, it is becoming increasingly clear that EPs also reflect parallel processing. Serial decisions may be accompanied by parallel memory storage, memory retrieval, set adjustments, and motor processing. Parallel processing is indicated by the occurrence of components overlapped in time at a single electrode location and by observation of independent components occurring at the same time but with different scalp distributions.

High-frequency far-field components, thought to originate in auditory nerves and various levels of brainstem, can be recorded at vertex for an auditory stimulus. These potentials originate mainly from the high-frequency end of the cochlea and carry information concerning stimulus intensity. Woods and Hillyard (this volume) failed to find evidence of peripheral gating in brainstem potentials evoked by probe stimuli in a dichotic listening task demanding selective attention. There are, however, animal EP data that suggest efferent gating at the brainstem level.

Components related to the initial registration of stimulus information at the cortex have been identified

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[2] Dr. Tueting is now at the Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland Medical School, Baltimore,MD. Dr. Tueting organized the correspondence, wrote the narrative summary, and edited this section. She was, however, unable to attend the Congress. Dr. Hillyard chaired the panel discussion in her absence.

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in the somatosensory and visual modalities. These components also carry basic information related to stimulus parameters such as intensity, wavelength, and spatial location, and are affected very little by the attention state of the organism, by the arousal-sleep continuum, or by decisions regarding stimulus input.

The primary registration of information at cortex is only the beginning of the perceptual-cognitive evaluation involved in the ultimate use, nonuse, or storage of stimulus information. The task of the Information Processing group of the EPIC IV Congress was to consider some of these later information processing decisions in a realm that is often referred to as cognitive.

Early components and selective filtering

At the conference, Hillyard defined a selective attention experiment as one involving a situation in which there are at least two stimulus categories. Selectivity is demonstrated when the subject processes one of these stimulus categories more effectively than the other, as indicated by a behavioral measure. For example, selective attention is demonstrated when the subject makes more accurate and more refined discriminations in one stimulus category than in another, reacts faster to one category than to another, or is able to retrieve from memory one stimulus category better than another. McCallum pointed to the unfortunate tendency to use the term selective attention without defining a specific operational context. Behavioral validation in EP experiments of selective attention is often nonexistent or inadequate.

Hillyard and his colleagues are now using concurrent signal detection measures of attention in their dichotic listening tasks. In a dichotic listening task, the amplitude of N100 is larger for relevant stimuli possessing easily identifiable characteristics such as pitch or spatial position toward which the subject's attention has been directed–usually by instructions and task. N100 amplitude is correspondingly smaller for stimuli occurring in irrelevant, rejected channels (Hillyard et al. 1973, Schwent and Hillyard 1975). These findings have been most clearly demonstrated when channels are separated by both pitch and spatial attributes (Schwent et al. 1976) and when subjects are exposed to information overload, i.e., when a subject is placed in a situation where there is difficulty in processing all of the input effectively in the time available.

Based on a study by Wilkinson and Lee (1972) involving auditory channels differing in stimulus frequency, Wilkinson has expressed the hypothesis that N100, and possibly N100-P200, of the auditory evoked response reflects selective filtering only for basic stimulus attributes like modality and location in space and time, but not for other attributes like pitch and linguistic distinctions. According to the hypothesis, contingent negative variation (CNV) resolution, rather than N100 itself, may reflect these latter categories of stimulus selection. However, Schwent et al. (1976) reported that selective effects on N100 could be obtained with either pitch or spatial location. Larger effects were found when both pitch and spatial cues were used. These results do not seem to be interpretable in terms of CNV resolution.

The conclusion that N1 is correlated with between channel (i.e. stimulus set) selection is based primarily on the work discussed above on the auditory vertex N100. At the conference, Hillyard proposed that the vertex N1 may index a cortical process related to an initial selection of a source of information for further processing regardless of modality–auditory, visual, or somatosensory. Hillyard's proposal assumes that an N1 component with a frontocentral distribution is elicited by stimuli in all three modalities. Measurement of N1 across modalities is complicated, however, by latency changes and component overlap. It is unclear whether auditory N1 has a frontal source, a temporal source, or both a frontal and a temporal source (Arezzo et al. 1975). Vertex N1 may be represented in occipital recordings at reduced amplitude, but N1 of the auditory evoked potential (recorded from vertex) and N1 of the visual evoked potential (recorded from occipital) may not be directly comparable. In the somatosensory modality, there is evidence that there may be an overlap of components originating in primary somatosensory cortex and in association cortex in recordings over either the vertex or the somatosensory region (Donald 1976).

Harter described selective attention in the visual modality. In the Eason et al. (1969) study, selective attention to spatially separate stimuli (light flashes presented to either the left or right visual field) was found to influence the amplitude of the first negative deflection of the occipital EP beginning 120 to 130 msec after the eliciting stimulus. These findings are consistent with Hillyard and Wilkinson's proposal that selective filtering is reflected by early components only when easily identifiable stimulus attributes are being discriminated. Harter and Salmon (1972), however, have reported selective attention effects on the earliest components of their visual EPs when the relevant and irrelevant stimuli were different colors with identical spatial attributes (but not when the relevant and irrelevant stimuli were in different orientations or were different shapes). Color is represented neurophysiologically in the peripheral visual system, while orientation and shape are represented at higher levels. Harter therefore suggested that it is the presence of peripheral representation of stimulus attributes, rather than the complexity of the attributes *per se*, that is a prerequisite to selective filtering.

A vertex negative component elicited by somatosensory stimulation has been described by Debecker and Desmedt (1971) and Desmedt and Debecker (1978). The findings with respect to the somatosensory vertex N1 are similar to the findings described above for the auditory and visual N1.

The P300 component

By far the most controversy and discussion in relating psychological variables to EPs has been generated by the P300 component, first described by Sutton et al. (1965). The P300 component is not modality specific and has been shown to be endogenous by the fact that it can be elicited in the absence of stimulation by an apparently internal trigger if (1) stimulus absence is significant and (2) stimulus absence is time-locked either by a prior stimulus or by some other time-marking aid.

A modality-specific negative component preceding the emitted P300 is elicited when stimulus omissions are rare in comparison to stimulus presentations (Simson et al. 1976). Therefore, this component is also an endogenous component. Mystery surrounds the question of whether the stimulus-elicited P300 is always preceded by a negative component or not—N2?, N190?, N250?, Nx?—but it is clearly evident in the waveforms of Harter and Salmon (1972), N. Squires et al. (1975) and others, and has emerged in principal component analysis (K. Squires et al. 1977). Part of the ephemeral nature of the negative component may be due to the fact that it is overlapped with other components known to occur in the same latency range when a stimulus is actually presented. If the latency variability of the negative component is the same as the latency variability for P300, then it would not be seen as easily as P300 because of the negative component's relatively small amplitude (Ritter, this volume). It is also possible that the negative component does not always accompany P300 but that the exact variables, subject or otherwise, necessary and sufficient for its elicitation have not been specified. So far, however, the N190 component seems to be affected by probability in the same way as P300 is, at least when both components are clearly elicited in target-identification situations (cf. K. Squires et al. 1977).

Karlin (1970) expressed the opinion that P300 represents a nonspecific reactive change of state subsequent to cognitive evaluation of significant stimuli. This opinion was originally prompted by the fact that P300 components tend to be elicited in situations where a slow negative expectancy process (CNV) precedes stimulus presentation. The CNV frequently resolves into a slow positive-going poststimulus process with recording, and this CNV resolution appears similar in some respects to P300. It was argued that any nonspecific state prior to the stimulus, a state indexed by EEG desynchronization (Naatanen 1967), or by nothing recordable from the scalp, could be associated with a nonspecific change of state subsequent to stimulus presentation and reflected in P300 (see also Näätänen 1975).

The existence of an independent P300 related to specific cognition and stimulus identification is no longer the issue. P300 components have been elicited under conditions of uncertainty when the stimulus delivers feedback concerning the accuracy of a guess or of a judgment, in situations where the subject is required to make a choice response as soon after stimulus presentation as possible, and in situations where low probability targets are presented against a background of more probable nonsignals. It has been shown by factorial experimental design and by scalp topography (e.g., Donchin et al. 1975) that CNV and P300 are dissociable components. However, the issue, in slightly different form, remains. It is probable that in some situations a distinct P300 and a positive CNV resolution (or "resident potential resolution") may be overlapped. Wilkinson suggests that baseline-to-peak measurements of P300 would ordinarily be confounded in these cases of overlap. (Random presentation of experimental conditions, although it does not eliminate overlap, does preclude differential prestimulus states, and should always be used in experiments aimed at poststimulus processing.)

How many "P300s"?

It would be more parsimonious if one unifying psychological construct could be found for the P300 component. A search for such a construct began several years ago after it was observed that P300 was elicited in a wide variety of situations. Uncertainty, information delivery, significance, salience, orienting, inhibition, selective recognition involving response set, and awareness have all been postulated as candidates for the one unifying construct for P300. (See Sutton et al., this volume). Donchin has postulated that P300 reflects the activity of a specific processor that can be invoked in a wide variety of situations. In this formulation (and most others), P300 latency would be determined by the time at which the processor is invoked (see Kutas and Donchin, this volume).

The trend now, however, is to search for more than one P300. Two is the current vogue in some circles, but three or more (P3a, P3b, P3 visual frontal, P3 no-go, P3 vertex) have been proposed. It is difficult to say at this point whether the seeming multiplicity of P300s simplifies the search for cognitive correlates of P300 or increases the complexity. Donchin, at the conference, argued for stricter criteria for admission to the P300 "club."

The criteria that have been used for isolating P300 components are scalp distribution and waveform characteristics such as latency and amplitude. Separation has been made on the basis of differences obtained in these measures for different psychological situations and for different modalities of stimuli. A P300, "P3a" is elicited by low-probability auditory stimuli presented while subjects are engaged in another task (e.g., reading) and "ignoring" the stimuli (Roth 1973, Ford et al. 1976, N. Squires et al. 1975, K. Squires et al. 1977). "P3a" has an early latency, relatively small amplitude, and a frontocentral scalp distribution. A P300, "P3b," elicited by low-probability signals in a vigilance task is later in latency, larger in amplitude, and has a centroparietal distribution. "P3b" has a virtually identical scalp distribution in a wide variety of target-detection tasks involving threshold-level stimuli, omitted stimuli, and auditory and visual discriminations (Hillyard et al. 1976; Picton and Hillyard 1974; Ritter et al., in press). Courchesne et al. (1975) reported a P300 to novel visual stimuli that were not task-related. This frontal P300, which had a relatively long latency, habituated quickly as novelty decreased. Although this P300 was also elicited by low-probability stimuli unrelated to the subject's main task and had a frontocentral distribution, it was not necessarily considered to be equivalent to the auditory "P3a." The "P3b" may or may not be identical to the original P300 described by Sutton et al. (1965), which is elicited in guessing situations and tends, if anything, to be a little larger at vertex than at parietal loci. The "detection potential" described by Cooper et al. (this volume) is also similar to "P3b."

There is speculation that the frontal P300 to both auditory and visual irrelevant stimuli may be related to orienting. The idea is that subjects will orient to low-probability stimuli even though they are told to ignore them and are involved in a task with other stimuli. The parietal P300 on the other hand has been related to delivery of relevant information, "response set," and decision. It is elicited by low-probability target stimuli to which a specific response such as counting has to be made. Ford has distinguished the two P300s within an active-attention versus passive-attention framework. The term "passive attention" might apply to the frontal P300 since attention is drawn involuntarily by a low-probability stimulus that is irrelevant to the subject's main task. The parietal P300, however, seems to require active attention, being obtained mainly when subjects are actively engaged in a task in relation to the eliciting stimulus.

A frontal P300, which may be related to response inhibition rather than orienting, was proposed by Papakostopoulous (Donchin 1976) for the Bristol Congress on Event Related Slow Potentials. A P300 with a frontocentral distribution similar to that of "P3a" (but much longer in latency) is elicited to the no-go stimulus in a go/no-go reaction time task (Tueting and Sutton 1976; Ritter et al., in press; McCallum 1976). The P300 elicited by the go stimulus has a more parietal distribution, reminiscent of the task related "P3b." In a choice-reaction time (RT) task, the subject is prepared to react as fast as possible to a stimulus, and the no-go stimulus can be considered to set up a red flag, i.e., an inhibition of the go. However, extending the construct of inhibition for P300 beyond choice-RT situations requires viewing motor functioning as a largely covert activity that is closely intertwined with cognitive processing (cf. Sokolov 1972 or McGuigan and Schoonover 1973).

The group generally agreed that latency by itself should not be used to dissociate P300 components. More information about the range of responsiveness of the P300 component to experimental variables and about the implications of component overlap at various electrode locations is needed before latency alone can be used to dissociate P300 components. Some of the problems involved in interpreting scalp distribution data are reviewed by the Scalp Distribution group (Donchin, this volume).

Moreover, it is still unclear whether several independent P300 components truly exist, and the issue of one versus several P300s was a focal point of discussion at the conference. The issue is reviewed in detail by Roth (this volume). The concept of only one P300 is still viable. Some of the findings interpreted as indicating multiple P300s could be interpreted as indicating one P300 whose anterior-posterior amplitude distribution varies with task demand. In addition, the amplitude of "P3a" is often small, and K. Squires et al. (1977) reported that "P3a" is an elusive component relative to "P3b." A further problem for the multiple P300 theory is that differences in anterior-posterior distribution could be a result of differences in the overlapping slow wave component as suggested by N. Squires in the correspondence. The slow wave has been reported to be negative-going frontally and to become progressively more positive-going parietally. Conceivably, P300 latency could also be affected—P300 could be truncated in latency frontally by the negative slow wave and lengthened posteriorally by the positive slow wave.

A note of caution should be mentioned in comparing observations of P300 latency from different laboratories. A lower cutoff frequency may influence P300 latency. In the correspondence, Rohrbaugh pointed out that P300 peak latency is sometimes shortened appreciably with a 1-Hz cutoff compared to a dc recording, reflecting phase shifts at frequencies near the low edge of the bandpass; its amplitude may also be reduced. However, it is unclear whether raising the low-frequency cutoff decreases the apparent P300 latency because of phase shifts of the P300 itself or because the concurrent slow wave is not passed by the filter.

P300 and orienting

The construct most frequently associated with the frontal P300 at present is orienting (see review by Friedman, this volume). The frontal P300 that follows novel visual stimuli may be a stronger candidate for an orienting correlate than the auditory "P3a" since it increases with the complexity/nonrecognizability of the stimulus and habituates rapidly (Courchesne et al. 1975). Friedman pointed out in the correspondence that orienting is reduced or absent in patients with frontal lobe damage (Luria 1966), and this is consistent with an orienting construct for the frontal P300.

One way to assess the validity of this hypothesis will be to record traditional autonomic measures of orienting such as heart rate, galvanic skin response, vasodilation of the skin, pupil, etc., in conjunction with EPs. Friedman et al. (1973) have studied event-related potentials (ERPs) and pupil dilation concurrently. They found situations in which dilation and ERPs correlated in response to psychological variables. For example, both vertex P300 and peak dilation of the pupil were monotonic inverse functions of stimulus and guessing probability. Roth et al. (this volume) have recorded auditory EPs and skin conductance concurrently, but their results were equivocal.

A significant methodological problem in recording ERPs concurrently with autonomic measures is that autonomic measures have a much longer latency than most ERPs. Only certain paradigms involving long interstimulus intervals may be used. Another problem is that the relationship of autonomic variables to orienting is not completely clear, and complexities, particularly variations in recording techniques and individual differences in autonomic responsivity, arise. The data overload and complexities are increased even further when ERPs (latency, amplitude, and scalp distribution measures of several components) are added to the picture.

P300 and decision latency

One conceptual framework implicates the P300 and decision-making. Unfortunately, the exact nature of the presumed decision is not thoroughly worked out, but a common thread running through the different tasks that elicit P300 seems to indicate that a comparison of stimulus input against representations in memory (templates) is involved either directly or indirectly. P300 is not directly involved in the decision regarding the selection of a specific motor response to a stimulus, as the large P300 obtained in choice-RT studies might imply, since large P300s are routinely obtained in a guessing task where subjects are not required to choose one overt response over another in the immediate poststimulus period. Similarly, specific poststimulus response selection is not involved when P300s are obtained with stimuli delivering feedback concerning accuracy in a discrimination trial or with non-task-related low-probability or novel stimuli. However, Hillyard pointed out in the correspondence that a theory relating decision-making to P300 must take into account the finding of Karlin and Martz (1973) that low-probability responses, as well as low-probability stimuli, are associated with larger P300s.

The appeal of the term "decision" is its generality, but a useful feature is that a decision is made at a precise point in time that is measurable, at least theoretically. Both N. Squires et al. (1975) and Roth (1973) found that P300 evoked in an orienting response situation occurs earlier than the P300 evoked in a signal-detection paradigm. It seems reasonable that the decision to orient is easier and faster than the decision that the target signal just occurred, and P300 latency could be reflecting that difference in decision time, a possibility suggested by Ford in the correspondence. However, since there is no voluntary intention when P300s are elicited by low-probability events presented while subjects are reading, Roth pointed out that it might be clearer semantically in this case to use the term "reaction" instead of "decision." Thus, the term decision may be more appropriate for the parietal task-related P300 than for a frontal orienting P300.

In the correspondence, Donchin pointed to findings relating P300 latency to an internal trigger, which varies with stimulus evaluation time (e.g., Kutas and Donchin, this section). The fact that P300 can be elicited without a stimulus also supports the idea that the latency of P300 is related to the latency of a cognitive event. Assuming that the trigger for P300 is basically internal, considerable variability in P300 latency across conditions in averages time-locked to stimulus presentation should be expected, and has been observed. Variability from trial-to-trial within a single condition, and variability among subjects in P300 peak latency distribution has also been noted. "Inexplicable" results when conditions that are stimulus time-locked (e.g., "hits" in threshold signal-detection paradigms) are compared to conditions that are not time-locked (e.g., "false alarms" in signal-detection paradigms) are also to be expected. Threshold signal-detection data become more interpretable when time marking aids are used (K. Squires et al. 1975).

Validity of latency measures: A first consideration in relating P300 latency to decision latency should be whether a difference in P300 latency is a valid measure. It is relatively simple to say that at a given latency there is an amplitude difference, but more assumptions may be involved in concluding that a component of assumed amplitude, shape, and approximate latency shifts peak latency as a function of condition or electrode location. Donchin has repeatedly pointed out that it may be misleading to identify components with the appearance of visible peaks in the waveform, and it may be preferable to define components in terms of the effects of experimental variables on voltage measurements.

Most of the group felt that, despite considerable problems, latency can be a valid measure. In fact, amplitude measures may also be invalid or confounded. For example, a condition with greater variance in peak latency distribution may result in smaller average amplitude because of high latency variability and not because of a real decrease in amplitude (Ruchkin and Sutton, 1978). One solution to the problem of the validity of amplitude and latency is to obtain amplitude distributions and latency distributions on a trial-by-trial basis. This, although more difficult to do for small components, is a possibility for P300, which can be fairly large on individual trials in some subjects.

The technical problems involved in defining P300 latency in individual trials are considerable however (see correspondence summary on Alternatives to Signal Averaging, by Weinberg). The problems develop from the low signal-to-noise (S/N) ratio for P300 at the scalp, which may be so low for some subjects and for some experimental conditions as to make single trial analysis an impossibility.

Typical single-trial analysis procedure for obtaining P300 peak latency and amplitude distributions involves setting a latency search window for a computer instructed to select the most positive peak within the time span specified. The selection of the search window is critical—too wide a search window may result in loss of the peak in some trials. A painstaking visual inspection of the data (and often of individual trials) before selecting a latency search window is often necessary. Ruchkin is now using Woody filter analysis (Woody 1967), which requires an iterative correlation procedure as a basis for realigning single trials before latency-corrected averaging. This procedure is more quantitative and objective than visual inspection or peak selection within search windows.

Other single-trial techniques do not yield peak latency information, although the latency at which there is an amplitude difference may be identified and experimental trials classified. For example, K. Squires and Donchin are using the value of a discriminant score on each trial. Researchers unable to deal with single-trial analysis may nevertheless obtain some information from additional measurements like breadth of P300, area of P300, rise and fall of P300, and onset latency of P300. Specific *post-hoc* clustering of the data may be helpful, e.g., clustering EP trials on the basis of differing ranges of reaction time.

Despite problems involved in single-trial analysis, the initial findings are intriguing. Ritter et al. (1972) found that variation in parietal P300 latency from trial to trial correlated with trial-to-trial variation in RT. Ruchkin and Sutton (1978) found that P300 varied in latency from trial to trial in a guessing task. In their study, latency variability was considerably greater when stimulus omission rather than stimulus presence delivered information concerning the subject's guess. Presumably, the point in time at which the subject decides whether a guess is correct or not (and hence P300 latency) is more dependent upon time-estimation ability in the omitted-stimulus case than in the present-stimulus case.

Validation of decision latency: Donchin pointed to a significant problem, namely that a method has not been developed to independently determine the time of invocation of the processor that P300 presumably represents. For example, Ruchkin found a tendency, not statistically significant, for emitted P300 latencies to be longer for incorrectly guessed single-click trials than for correctly guessed single-click trials. (Subjects guessed whether a single or a double click would be presented on each trial, and a P300 was emitted at the point in time of omission of the second click in a single-click trial.) One possible inference is that subjects may wait longer to acknowledge the absence of a second click when they have predicted that it would be present. Testing this plausible inference directly is a difficult problem, as Ruchkin pointed out. (A similarly delayed P300 for feedback that disconfirmed a prior judgment was found by K. Squires et al. 1973a.)

Psychologists have traditionally made inferences about cognitive events via behavioral measures, and the traditional behavioral measure of decision latency has been RT. The correspondents all agreed to take seriously the caution to record physiological and behavioral data in the same set of trials; Sutton (1969) outlined the very good reasons for doing this. A major problem arises, however, because potentials preceding and following the response may be overlapped (especially in the centroparietal area) with potentials related to stimulus evaluation (decision). These "motor" potentials consist of a slow premotor negative potential, a higher frequency complex associated more directly with response initiation, and then a large and slow postresponse positive wave peaking about 150 msec after response (thought by some to be related to somatosensory feedback from muscle and joint receptors). In an RT task, premotor potentials overlap evoked potential components up to the point of the reaction, and for fast RT, the postresponse positive wave could overlap P300, N350, and P400.

A further complication emphasized by Roth and by Wilkinson is that motor involvement increases the size of the CNV, and they point out that the timing of decision may be more closely associated with the latency of CNV resolution than with the latency of P300. In any case, it is likely that in some instances the latency and amplitude of CNV resolution and the latency and amplitude of P300 will be confounded by the overlap of these two components.

Some correspondents emphasized that it may prove impossible to disentangle decision-related components like P300 from motor components associated with a required reaction. Simple linear addition of motor components when an RT task is added to a situation is unlikely. However, the advantage of having an independent behavioral measure of decision latency is so important that investigators are compelled to use a number of strategies that converge on this issue. Several techniques considered in this context follow:

1. Choice of response measure in RT studies. The judicious choice of response measure in RT studies may help in reducing motor potentials and movement artifact. In a study of the relationshp of EPs and RT to uncertainty, Tueting and Sutton (1976) found that a lift no-lift response task gave cleaner response-evoked potentials than a key press response. Rohrbaugh suggested that systematically varying force and excursion of the responding member may aid in partialling out motor responses, and that, in many experiments, keeping force and distance at a minimum may reduce motor potentials. Stretching this strategy even further, it may be possible to train subjects to make an extremely small response that can still be picked up by EMG recording. Covert verbal reactions such as counting to onself should be throughly investigated to see if minute muscle or laryngeal responses can be picked up reliably, since counting should be considered a motor response and may be accompanied by motor potentials and motor artifact. Whatever the response elected, it should be absolutely silent and should produce as little tactual and visual sensation as possible to avoid inadvertently adding sensory EPs to the already complex picture.

2. Differential topography. In come cases, motor potentials can be separated from stimulus-evoked responses by precise delineation of topography (Vaughan et al 1965, Vaughan et al. 1968) and some motor potentials have been identified by their asymmetry (Kutas and Donchin 1974). Possibly a factor analysis approach using data from several recording sites could separate "motor" and "cognitive" effects, but factor analysis assumes an underlying linearity, which according to Ruchkin may not exist in this situation

3. Delayed response control. A delayed-response task (or a task requiring no motor response) can be compared to an otherwise identical RT task (Vaughan et al. 1965, Karlin and Martz 1973, Picton et al. 1974, Courchesne 1975). However, Roth pointed out that delaying or omitting motor responses is likely to change the nature of the decision and other cognitive features of the task. A delayed-response control would be better than a no-task control, as long as anticipatory reactions are prevented.

4. Self-paced motor response control. Another strategy is to collect self-paced motor responses in a separate control condition. Potentials obtained in the self-paced condition can be inspected and inferences drawn (Ritter et al. 1972), or the motor potentials obtained in the self-paced task can actually be subtracted from the potentials obtained in the RT task. Presumably, subtraction would leave potentials related to stimulus evaluation (decision) without motor confounding. The subtraction procedure assumes, however, that the motor potentials in RT situations are similar to motor potentials recorded in self-paced response tasks. Several correspondents pointed out that self-paced tasks may differ in a number of ways from the task for which they are being used as controls. For example, Ruchkin et al. (1977) used self-paced motor responses as a control in a time-estimation study.

5. Comparison of stimulus versus response-locked potentials. Averages time-locked to the response can be compared to averages time-locked to the stimulus (Ritter et al. 1972, Karlin et al. 1971). Presumably, decision time would be more closely related to actual response time that to stimulus onset time; therefore P300 should be more precisely time-locked to response time. The experimental findings to date are equivocal (Karlin et al. 1971), indicating that P300 may actually be smaller in response-locked averages than in stimulus-locked averages. However, motor potentials are more closely time-locked to response time, and motor potentials can be seen more clearly in response-locked averages than in stimulus-locked averages.

6. The go/no-go reaction time task. Still another technique is to use a go/no-go choice-RT task, and to counterbalance conditions (usually within subjects) so that every condition has a replicate (one go and one no-go). The assumption is that no-go evoked responses are not confounded with motor potentials since a motor response is not required. However, it seems likely that there is motor involvement in the no-go case in a choice-RT task. For example, motor response inhibition in the no-go case could be reflected in a motor potential related to motor inhibition. Specifically, frontal P300 is a candidate (Donchin 1976; McCallum 1976; Ritter et al., in press; Tueting and Sutton 1976).

P300 latency and RT: If P300 occurs in precise temporal relation to a cognitive decision, an independent behavioral measure of decision latency such as motor RT ought to correlate with P300 latency. Hillyard, for the correspondence, reviewed studies in which P300 and RT were recorded concurrently. Only two of the studies indicated that RT variations paralleled changes in P300 latency (Ritter et al. 1972, Picton et al. 1974). A few other studies provided less direct support for a positive P300 latency-RT correlation (Bostock and Jarvis 1970, Rohrbaugh et al. 1974, Routh et al. 1975, Posner et al. 1973). On the other hand, many studies showed a dissociation of P300 latency and RT (Karlin et al. 1970, Karlin et al. 1971, Karlin and Martz 1973, Donchin et al. 1973, Donchin et al. 1975, Parasuraman and Davies 1975, Courchesne 1975, Ford 1975).

Admittedly, these studies suffer from problems discussed above, such as confounding from component overlap, and from problems in comparing mean RT to peak latencies obtained from evoked potentials averaged over trials (rather than from single trials). Despite these shortcomings, the inconsistencies are too great to dismiss. The dissociation between RT and P300 latency seems to be separable into the two following categories.

1. P300-reaction time correlations in relation to discriminability and equivocation. Ruchkin and Sutton (this section) have formulated the concept of equivocation in relation to P300. Equivocation refers to a loss of information related to the subject's *a posteriori* uncertainty, and can be thought of in terms of the "immediacy and ease" with which a decision can be made. An increase in equivocation leads to a decrease in P300 amplitude. The equivocation concept is in some ways similar to the "confidence of the decision" concept proposed by K. Squires et al. (1973b).

Dissociation between P300 latency and RT seems to occur when discriminability, or equivocation, is the variable. Both P300 latency and RT increase as equivocation increases, but the magnitude of the change appears to be three to five times greater for RT than for P300 latency. For example, Ford et al. (1976) varied the degree to which rare target tones differed in frequency (pitch) from more probable background stimuli. As the frequency difference decreased (increasing equivocation), P300 latency increased by an average of 26 msec while RT increased by an average of 81 msec. Parasuraman and Davies (1975) found that P300 latency and RT were greater for false alarms as compared to hits in a vigilance task, but the magnitude of the difference was greater for RT than for P300 latency.

2. P300-RT correlations in relation to uncertainty and probability. The second kind of dissociation is more serious for the hypothesis that P300 latency is a measure of decision latency. This kind of dissociation seems to come about whenever equivocation is low but uncertainty or probability is the variable. (In information theory, a low-probability stimulus has greater uncertainty than a high-probability stimulus.) As uncertainty increases, P300 latency remains the same (or it may even decrease), while RT increases by a considerable amount (Hyman 1953). The situation is further characterized by the fact that the increase in RT often is accompanied by an increase in P300 amplitude. For example, when comparing a condition where the subject does not know in advance what stimulus will occur next to a condition where the subject does know, RT increases considerably with the added uncertainty, but P300 latency does not. P300 amplitude may increase (Tueting and Sutton 1976) or not (Donchin et al. 1973), apparently depending upon other factors such as pressure for fast RTs. Hillyard suggested that these dissociations between RT and P300 latency when uncertainty (or probability) is the variable could represent a disruption of motor processing as a result of the emotional concomitants of the added uncertainty or by some other confounding of decision latency with probability.

The theory that P300 is directly related to a decision involving response selection encounters still another obstacle. It has been reported that the peak of the parietal-occipital P300 component in a particular trial can occur, under certain circumstances, after the subject's reaction in that trial (Eason et al. 1969, Ritter et al. 1972, Rohrbaugh 1973). The finding that P300 latency can occur after the reaction indicates that the correlation between parietal P300 latency and decision latency is not a causal one. Ritter (this section) concludes that even P300 onset cannot be causal to reaction when the time between the initiation of motor processes in the brain and RT is precisely considered.

In summary, the theory that P300 latency is directly related to an independent RT measure of decision latency runs into trouble. There are reports that P300 latency and RT can be dissociated, that response-locked averaging can result in a smaller P300 than stimulus-locked averaging, and that the peak of P300 can occur after the reaction.

A casual relationship between P300 and reaction can probably be excluded, but P300 may still be indirectly related to response selection. Hillyard suggested that RT-P300 latency dissociatons could be explained if P300 reflects an early decision such as "the stimulus belongs to a relevant class" rather than to a later decision such as "which stimulus it is and what response is required"; subjects may hold off a "one of a relevant class decision" until a target is detected with low-probability targets, but not hold off with frequently occurring targets. Alternatively, the P300 could simply represent a phasic arousal process related to the consequences of the decision. Simson et al. (1976) have proposed that P300 could be related to "conscious awareness of the outcome of the decision." Finally, P300 could reflect adjustments of memory representations and set that are consequent to the decision on the current trial but may be reflected in decisions on future trials (see section below on Feedback and P300).

Ritter concluded that P300 does not reflect the selection of a particular target within a class of stimuli in vigilance tasks because (1) P300 follows rather than precedes reaction time and (2) stimulus probability appears to be a more potent variable than whether or not the stimulus is a "target." Ritter (this section) proposes that the earlier negative component may be more directly related to decision latency than is P300.

P300 and template match/mismatch

Decision processes are no doubt different for the different tasks that elicit P300 (guessing, feedback, detection). An underlying feature, however, could be a match/mismatch judgment (Ritter and Vaughan 1969, K. Squires et al. 1973a, Posner et al. 1973, Thatcher 1977) involving comparison with a template stored in memory. One proposal is that mismatch involves extra processing time compared to match. RT is shorter for match than for mismatch judgments, and Posner et al. (1973) have reported that P300 for match judgments occurs earlier than P300 for mismatch judgments. A second proposal is that match judgments are accompanied by a larger P300 because the stimulus fits a representation stored in memory. The fact that P300 amplitude is larger for match than for mismatch judgments in auditory threshold tasks (Hillyard et al. 1971) and in semantic tasks (Thatcher 1976) supports this latter proposal.

The problem is that the above match/mismatch premises do not hold when probability is the variable. RT results are consistent in that RT is shorter for a high-probability stimulus (match) than for a low-probability stimulus (mismatch). However, P300 results do not fit–P300 components recorded for a high-probability stimulus (match) in identical tasks are smaller in amplitude and equal, or even later, in latency than for a low-probability stimulus (mismatch) (Tueting 1968, Friedman et al. 1973, Ritter et al. 1968, Ford 1975).

According to orienting response theory, the template is inferred to be for a high-probability stimulus because of its greater frequency and familiarity (Lynn 1966). In an orienting response framework, a low-probability stimulus is viewed as a mismatch because it is unexpected, and Ritter and Vaughan (1969) have proposed that P300 represents additional perceptual and cognitive processing called in to evaluate the significance of a mismatch. Mismatches in orienting response theory usually involve low-probability stimuli that are also novel. With the exception of Courchesne et al. (1975), however, low-probability stimuli in EP studies have not necessarily been novel.

In summary, RT results are consistent in that RT is longer for mismatch, which corresponds to the hypothesis of longer processing time for a mismatch. However, there seems to be a paradox for P300 amplitude and latency. For threshold and semantic-meaning tasks, a match is related to a larger amplitude, earlier latency centroparietal P300. However, for probability situations, a match is related to smaller amplitude and equivalent (or later) latency P300 (frontal and parietal).

Donchin proposed that some of the critical questions concerning match/mismatch theory are "How do we infer what the template is?" and "Why are some templates singled out for association with P300 while others are not?" One way out of the paradox is to postulate two different match/mismatch processes for P300, one for probability (frontal P300?) and one for more complex target-detection tasks (parietal P300?). In addition, low-probability events are inherently more significant to the organism than high-probability, familiar events, even if the task does not specify them as targets. Some developmental theorists have proposed that infants learn by attending more to events that are lower in probability and slightly discrepant (e.g., Kagan 1972). In a certain sense then, low-probability events are target-like, and it is clear that P300 is elicited by target events. The inference of a template for low-probability events on the basis of their inherent target-like nature would have the advantage of fitting all of the P300 results into the same match/mismatch logic. Note, however, that RT results would not fit the notion of a template for low-probability stimuli-RT is longer for low–than for high-probability events.

Because inferring what the template is, or how many templates there are, may be difficult, as the above discussion demonstrates, progress may be made in using experimental designs specifically aimed at memory search (cf. Roth et al. 1975, Posner et al. 1973, Thatcher 1976, Poon et al. 1976). Roth's design involves storage of specific templates with subsequent probing of memory for the template. An analysis of the relationship between P300 and template match/mismatch has been made by Ford (this section).

P300 and feedback

Dissociation between P300 latency and RT, the finding that P300 can occur after the response, and the fact that response-locked averages can attenuate P300 bring into question the generality of the decision construct for P300. The decision concept can be reconstructed, as Donchin has done, if the argument is made that P300 may not be so much related to decisions of response selection in the current trial as to modifications that will be reflected in decisions in future trials. This view of P300 is supported by the fact that large P300s are obtained to stimuli delivering feedback concerning guessing outcome or discrimination-task accuracy, and to low-probability or novel stimuli requiring no task whatsoever. Response selection is not required immediately following stimulus presentation in these situations. However, stimulus information in these cases may influence future guesses, future judgments, or future reactions to the same novel or low-probability stimulus. In this conceptualization, stimulus presentation elicits a readjustment of templates or relative probabilities, reevaluation of relative costs of subsequent decisions, etc. For example, Donchin suggested that the sensitivity of P300 to probability could reflect the greater need for readjustment following the presentation of a rare event.

In a guessing task, response selection occurs before stimulus presentation; therefore, the fact that a large and reliable P300 is elicited implicates P300 involvement in feedback. Feedback can be inferred here in terms of its information properties, i.e., the subject finds out whether his guess was right or wrong. If he made a high-risk guess, the feedback may be interpreted differently than if he had made a low-risk guess (Tueting and Sutton 1973).

In a guessing situation, P300 is larger to sound after light (crossmodal) than to sound after sound (ipsimodal), and the same is true for light (Levit et al. 1973, Zubin and Sutton 1970). These results correspond to RT data; crossmodal sequences yield longer RTs than ipsimodal sequences (Waldbaum et al. 1975). Pilot data also suggested that P300 amplitude in the current trial depends upon whether the subject's guess in the previous trial was right or wrong (Sutton, unpublished data).

Tueting (1968) and Tueting et al. (1970) reported that P300 in a guessing task was large for a low-probability event whether the event was determined in terms of stimulus probability, sequential probability (probability of alternation or of repetition), or probability of the outcome of the subject's guess. These effects were strongest for correct guess outcomes, and there was some indication that probability of outcome was an additional relevant factor. The fact that the probability effect held for probability of repetition as well as for probability of alternation and the fact that the probability effect differed for right and wrong outcomes indicates that sequential effects for P300 are not a simple function of time separating identical stimuli in a sequence, and hence are not a result of recovery or simple habituation. These sequential effects, however, could be related to cognitive variables such as the subject's running calculation of absolute and sequential probabilities of events and of the calculated risks involved in making one guess rather than another. The right-wrong dimension in the guessing task can be interpreted within a match/mismatch framework, and templates for probability and analysis of risk can be inferred to develop in probability learning tasks (Leifer et al. 1976).

K. Squires et al. (this section) have investigated sequential P300 effects in a random program of rare target stimuli and frequent background stimuli. These effects go back in sequence at least 10 stimuli (or 11.7 sec) when the probability of the target is 10% and the probability of the background stimulus 90%. The results indicate that a stimulus elicits a larger P300 if preceded by more of the same than if preceded by different stimuli. A similar result has been reported by Barrett et al. (1975) in a threshold situation.

A more complete discussion of the relationship of P300 to feedback can be found in Sutton et al. (this section).

Summary

Conference discussion confirmed the fact that evoked potentials (EPs) reflect a number of cognitive variables in a systematic manner. Discussions revolved around three EP components: N1, P300, and a negative component preceding P300. The latter negative component is similar to P300 in that it too is endogenous, but unlike P300, it is modality specific.

Evidence is accumulating that N1 is related to stimulus set, an early stage of selective attention, in auditory, visual, and somatosensory modalities. However, most data have come from studies using auditory stimuli. The level of attenuation or gating in the nervous system, whether central or peripheral, and the amount of attenuation in terms of the complexity of the information being processed were debated. One aspect emphasized was the importance of precise definition of selective attention based on behavioral measures, preferably obtained on the basis of signal detection theory.

The relationships of P300 to response set, selective attention, decision, feedback, expectancy, orienting, uncertainty, etc., were discussed. The focus was on the proper methods for relating two sources of data—on one hand, behavioral data on cognition, and on the other hand, EP data. One important behavioral paradigm for measuring the time required for various mental operations, reaction time (RT), was discussed at length. Certain methodological issues arise when comparing RT data to EP data. Consequently, there is considerable difficulty in making sense of the relationships between RT, P300 latency, and P300 amplitude that have been obtained to date. Much theorizing in the area of cognition involves the notion of a comparison of stimulus input against stored memory representations. In this context, the usefulness of the match/mismatch logic for interpreting P300 was assessed, and the difficulty of defining the template was pointed out.

The negative component preceding P300 received a great deal of attention. At the present time, data related to this new component are limited, but discovering where this component fits in human cognition is an important challenge for future study.

There is considerable data and theory in cognitive psychology that EP researchers could use to advantage in designing experiments and interpreting results. EP data may well prove fruitful for an increased understanding of the area of cognition as well. EPs may serve to validate inferences made on the basis of behavioral measures concerning what intervenes between stimulus input and response output. In any case, it seems likely that these two areas of investigation—cognition and evoked potentials—should eventually mesh. For the time being, any contradictions are likely to be particularly fruitful areas of research.

HOW MANY LATE POSITIVE WAVES ARE THERE?[1]

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Three variables define the relatively faceless phenomena to which our research efforts are devoted: voltage, time, and location. The interactions of voltage and time that create peaks with various latencies and polarities give a name to the topic of this discussion late positive waves (LPWs). This family of waves has also been called collectively P3 or P300. The latter term, which implies a mean latency of 300 msec, is increasingly less descriptive as later and later LPWs are reported. If the term LPW is reserved for waves after P2, a rather flexible minimum latency must be accepted for LPWs. The P2 component in the auditory mode has mean latencies that vary at least from 170 to 205 msec, depending in part on task parameters (Roth et al. 1976a). Visual P2s are later, extending to around 280 msec. Thus, the earliest LPW, P3a, is sometimes hard to distinguish from P2. The P3a component may merge with P2 or it may be as late as 300 msec (Roth 1973; N. Squires et al. 1975; Snyder and Hillyard 1976; Ford et al. 1976). It is seen most clearly when stimuli are rare and task-irrelevant. The P3b component usually occurs in the 300- to 400-msec range for rare task-relevant stimuli. P3b is the standard P300 described in many earlier papers by Sutton, Donchin, Tueting, Hillyard, and others. A "positive missing stimulus potential" appears when stimulus omissions from a regular stimulus train are rare and when these omissions are targets (e.g., Simson et al. 1976). In the Simson et al. experiment, this wave had a mean latency of 465 msec for auditory stimuli and 565 msec for visual stimuli. A peak termed "P4" with a latency of 650 msec has been reported by Picton et al. (this volume). It was elicited by an auditory feedback stimulus that gave information as to the correctness of a choice in a visual concept learning task. Finally, Courchesne (1976) found that rare task-relevant visual targets that evoked a positive wave at 417 msec in adults, evoked a similar wave with a mean latency of 702 msec in 5- to 8-year olds. Equally rare but nontarget stimuli evoked a positive wave with a mean latency of 448 msec in adults and 982 msec in the children.

The components listed above can be called "peaks" since they rise and fall in a few hundred milliseconds. A late slow positive wave at Pz has been observed to follow rare task-relevant stimuli. It begins some time after 300 msec and lasts for more than 1 sec (N. Squires et al. 1975, K. Squires et al. 1977, N. Squires et al. 1977). Either CNV resolution or skin potential artifacts at the reference electrodes can produce prolonged shifts, but these are unlikely explanations for the origin of this slow wave because of its scalp distribution.

Of the three variables that characterize the phenomena, location has become the most favored in arguments for the distinctness or unitary nature of the various LPWs. At least four different anterior-posterior scalp distributions have been described for these waves: (1) A predominantly parietal-central distribution ($Fz < Cz < Pz \gg Oz$) is characteristic of most peaks in the P3b latency range and missing stimulus potentials. (2) A predominantly frontal-central distribution ($Fz = Cz > PZ > Oz$) is said to be characteristic of the P3a component , or P3s to task-relevant stimuli to which no motor response is required (Hillyard et al. 1976, Tueting and Sutton 1976), and of unfamiliar rare task-relevant nontarget visual displays in adults (Courchesne et al. 1975), or of all rare task-relevant, nontarget visual displays in children (Courchesne 1976). (3) A parietal-occipital distribution ($Fz < Cz < Pz = Oz$) was found for "P4." (4) A distribution in which the polarity differs by lead was found for the slow wave. This wave is positive at Pz, almost absent at Cz, and negative at Fz.

If there are four topographic distributions of LPWs, does it follow that there are four different processes? If "process" is considered to be an explanatory framework that brings order to our observations, the distinctness of phenomena observed in a particular experiment cannot be considered sufficient evidence for the distinctness of the processes underlying them.

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Although there is an inherent ambiguity in grouping things as "like" and "unlike," an ambiguity similar to that of defining figure and ground for a pattern recognizer, certain guidelines are implictly followed in classifying evoked potential phenomena. First, distinct processes should be represented by phenomena that can be varied independently. Statistical procedures such as principal component analysis are of value here, but there are many pitfalls in determining the independence of phenomena. Some of these pitfalls are discussed by Weiskrantz (1968) in his critique of the concept of "double dissociation." Suffice it to say that processes related to each other in a hierarchical manner may appear to be dependent until just the right experimental manipulation is discovered. Second, processes are often thought of as distinct only if they are discontinuous and intermediate processes are never encountered. Whatever combination of voltage, time, and location define the two processes, phenomena should not fall into a continuous spectrum between the two definitions.

The criterion of discontinuity for distinctness can be made clearer by reference to a few examples. If four different auditory stimulus intensities resulted in four significantly different N1 amplitudes, no one would be misled into thinking that this was evidence that four different processes were operating, since N1 is known to be a continuous variable related to sensation level by a reasonably simple monotonic function. Thus, the four distinct amplitudes only represented the experimental parameters chosen. Or if LPWs of four distinct latencies were created, principal component analysis might yield four orthogonal components. It might even be possible to vary the amplitudes independently from the latencies. Yet, since available data suggest that latency is a continuous function of speed of stimulus evaluation, latency differences are not considered sure-fire evidence for distinct processes. For example, Kutas and Donchin (this section) found that LPW latency varied more than 200 msec, depending on how visually displayed words were to be evaluated. More complex evaluations that took more time, such as deciding whether one word was synonymous with another, resulted in later LPWs than simpler evaluations, such as identifying a fixed target word. Similarly, target stimuli that are more easily discriminable give shorter latency LPWs than less discriminable targets (N. Squires et al. 1977). Children probably take longer than adults to process stimuli, which could explain some of the longer latency LPWs for children found by Courchesne (1976). Even if age has an independent effect on LPW latency, it is likely to act continuously in that older children would have latencies intermediate between those of younger children and adults. The realization that LPW latency is a continuous variable makes it easy to accept the conclusion of N. Squires et al. (this section) that P3bs elicited by rare target stimuli of various intensities and by the omission of stimuli in a train are part of the same process or "functionally equivalent." These two LPWs have the same scalp distributions, are affected in the same way by manipulations of probability, and show discrepancies in amplitude and latency that could be explained on the basis of a continuous variable such as amount of time jitter or latency of recognition.

P3a presents more difficult detection and classification problems. It would be convenient if P3a were simply a very early LPW consistently elicited when stimulus-processing demands are minimal. Unfortunately, LPW latency is not always shorter when subjects are told to ignore stimuli or given a reading task (Roth et al. 1976b; and this section). K. Squires et al. (in press) had difficulty finding P3a in a replication of N. Squires et al. (1975). K. Squires et al. (in press) did find a factor that had peak loadings in the 250 msec range, but it accounted for only 2.6% of the variance and the factor scores were not consistently related to experimental variables. However, in spite of all these difficulties in specifying the exact circumstances under which positive waves with latencies between 200 and 300 msec can be produced, it is impossible to disregard the evidence that such peaks exist.

Evidence for the distinctness of P3a and P3b derives primarily from the different topographic distributions of the two components. This raises a question of the validity of topographical differences as criteria for establishing the distinctness of a process.[2] There is no logical priority for topographic distribution over amplitude and latency as a criterion of distinctness. The power of distribution as an argument for essential differences comes from the concreteness of being able to imagine generators at spatially distinct locations in the brain. In fact, different amplitudes and different latencies, even without different scalp distributions, may also be produced by different physical generators in the sense of different pathways and different selections of single units. However, these mechanisms are so poorly understood that they are not even a topic of speculation in the LPW literature. Just as differences in amplitude or latency do not necessarily imply different processes, neither do different distributions and different generators. Take, for example, the experiment of Kutas and Donchin (1974) in which the readiness potentials of right-handed subjects were larger over the hemisphere contralateral to the responding hand. Two distinct distributions occurred, each undoubtedly produced by spatially separated neural masses. The authors, however, never claimed that they had fractionated the readiness potential into two distinct processes, RPr and RPl, because the mapping of motor and sensory processes on the cortex relates asymmetry and task parameters in a fairly simple manner. The relationship is not completely continuous given the neuroanatomy of the cortex, although intermediate distributions might be obtained if the subjects pressed foot pedals. That is, the unity of a process may depend on structural and developmental considerations rather than the continuity of mathematical descriptors.

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[2] See the Scalp Distribution section of this volume for an extended discussion of related issues.

Similarly, a unitary LPW process that changes smoothly in latency and distribution depending on stimulus at processing time might be hypothesized. For instance, P3a and P3b could simply represent two samples of this function at different points in time. At early latencies, the process would be more frontal, and at later latencies, more parietal. Thus, latency and distribution would be dependent. Unfortunately, there is insufficient evidence to claim continuity.

Ford et al. (1976) did find distributions intermediate between P3a and P3b in an experiment where an attention variable had three levels. These results would have been more convincing if the amplitude of P3a had been larger. The flat anterior-posterior distribution obtained when attention was not directed to the stimuli may have been a floor effect related to the effect of noise on their measurement method. They located peaks as the maximum or minimum voltage in a specified latency range and, as the signal-to-noise ratio declined, noise peaks rather than signal peaks may have been detected. Thus, the peaks located would never be smaller than the "floor" of fluctuations produced by the noise.

Also damaging to the hypothesis of a single generator for P3a and P3b is the fact that, even within a single experiment, latency and distribution may be independent. Courchesne et al. (1975) reported the same latencies for LPWs with a frontal distribution elicited by complex visual displays and for LPWs with a parietal distribution elicited by simple visual displays (digits). However, these results do not justify postulating two distinct processes. Instead, these results suggest that experiments could be devised to test the distributional continuity of LPWs by varying stimulus familiarity. If a parameter were discovered that controlled LPW distribution continuously, a good case could be made for considering LPWs part of a single process.

Another type of implicit evidence for the distinctness of processes is the presence of visually distinct peaks in an evoked potential tracing. However, P3a and P3b are so close together, and P3a is so close to P2, that visual separation is not convincing. Even if two peaks were discontinuous in latency (i.e., never overlapping), multiple peaks could represent a single process that requires the repetition of a mental operation or a single process that yields multiple peaks because of its specific neuroanatomy (e.g., multiple parallel pathways). In these cases, principal component analysis would be helpful.

Even peaks that differ in both latency and distribution could represent the same process. This may be the case for the P4 wave of Picton et al. (this volume), which appears in their Fig. 5 to occur in the same tracing as an earlier P3. Both peaks are affected identically by the experimental variables. The authors conclude that "this distinction" (i.e., latency and scalp distribution differences) "makes it possible to hypothesize that the two waves reflect separate psychophysiological processes, possibly the appreciation of feedback information (P3) and its utilization in conceptual learning (P4)." Based on the available evidence, the authors' conclusions seem to be unwarranted. The peaks are highly correlated in appearance. The most logical argument would be for the authors to contrast their findings with those of the many other studies that have reported P3s without P4s. At best, this would open the possibility that the two peaks represent separate processes.

In general, the case for multiple LPW processes is unproven. More data are needed, particularly on the experimental parameters that affect late wave distribution. If other ERP processes play an interactive role, such processes may not be positive ones—i.e., interactions of slow negative processes with LPWs may change LPW distributions as well as latencies. For example, N. Squires et al. (in press) observed a 0.75 correlation between distributional differences in P300 amplitude and slow wave size, and a correlation of 0.86 between latency differences and slow wave size. Other negative phenomena have been reported by Loveless and Sanford (1974), Rohrbaugh et al. (1976), and Roth et al. (1976a). Rohrbaugh et al. described a frontal negativity that increased over time, a finding that could explain the observation by Courchesne et al. (1975) of LPWs that initially showed a frontal distribution, but shifted in a posterior direction across trials. The nature of these negative processes and their interactions with LPWs remain to be clarified.

LATENCY OF EVENT-RELATED POTENTIALS AND REACTION TIME

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Of the various event-related potentials (ERPs) elicited by target stimuli in reaction time (RT) experiments, the P3 component (hereafter assumed to have a parietal maximum) is the only one previously known to have a range in latency great enough to be related in time to RT. Depending on the experimental condition, the peak latency of P3 based on averaged ERPs has been found to vary anywhere from 250 to 600 msec. The range in latency for single-trial P3s for an individual subject within a single condition can be as great as 300 msec (Ritter et al. 1972). The large variability in P3 latency both within and across conditions is consistent with most theories concerning the functional significance of physiological activity underlying P3, such as information delivery, target selection, decision-making, sensory discrimination, and match-mismatch processes. (For review, see the summary of preconference correspondence, this section.) In addition, these theories tacitly or explicitly presume a correlation between P3 latency and RT. As Hillyard pointed out in preconference correspondence, some studies have found a correlation (e.g., Ritter et al. 1972, Picton et al. 1974), while others have not (e.g., Karlin et al. 1970, Karlin and Martz 1973). Kutas and Donchin (this section) have shown the correlation between P3 latency and RT is affected by the trade-off between speed and accuracy of response, a finding which may account for some of the discrepant results.

There is a more serious problem for most of the theories of P3 function than whether or not the latency of P3 correlates with RT. Ritter et al. (1972) concluded that P3 onset could occur early enough to be causally related to RT. That conclusion was based on estimated average delays for each subject between P3 onset and the initiation of motor activity in motor cortex. For one subject (WR), the estimated average delay was 20 msec; for other subjects, it was longer. It therefore appeared possible for P3 onset to precede motor activity, though it was suggested that the N2 component, which peaks about 100 msec earlier than P3, may reflect a significant factor in the timing of RT. In retrospect, it appears likely that a large proportion of motor responses must have begun before the onset of P3. Otherwise, the distribution of delays between P3 onset and the initiation of motor activity on single trials would have been surprisingly small in variability (an unlikely possibility since the correlations between P3 and RT latencies were generally in the 0.70s or were quite skewed). There is certainly no justification in hypothesizing that P3 reflects such processes if subjects can make discriminative motor responses prior to P3.

Several investigators have recognized that P3 occurs too late to reflect the processes usually attributed to it and have accordingly suggested that P3 reflects sequalae to task-related decisions and responses, such as registration of pertinent information in memory, resetting of perceptual analyzers, or other processes associated with preparation for future trials (Donchin et al. 1973, Picton and Hillyard, 1974). Since P3 apparently occurs too late to reflect target selection or information delivery, we turned our attention to N2, a component that occurs early enough in time to be causally related to motor responses, appears to be elicited in the same kinds of situations that elicit P3, and, like P3, is endogenous in nature.

There seem to be two reasons for the late arrival of N2 on the ERP scene. First, N2 is smaller in amplitude than P3 and is often obscured by P2 because of overlapping latencies of the two components. Second, since N2 is smaller in amplitude than P3, less variability in latency from trial to trial is required for N2 to be observed in averaged ERPs. Klinke et al. (1968) resolved both of these difficulties with one stroke by randomly omitting stimuli in a train of stimuli delivered at a steady, fast rate. The omitted stimuli elicited clear N2 and P3 components. The use of a steady, fast rate of stimulation presumably permitted subjects to develop internal rhythms that produced excellent time-locking of N2 to stimulus omissions. The circumstance that P2 (an exogenous potential) is not elicited by omitted stimuli prevented P2 from obscuring N2.

Two reports support the time-locking explanation. Picton et al. (1974) found that increasing the interstimulus interval in a train of stimuli which contains randomly omitted stimuli resulted in smaller and eventually unobservable N2 components associated with stimulus omissions. (A similar result occurred for P3, but it could still be observed at the longest interstimulus interval used because of its greater amplitude.) Ruchkin and Sutton (in press) have concluded that the failure to observe N2 for omitted stimuli that elicited P3 in Sutton et al. (1967) was due, at least in part, to the degree of trial-to-trial variability in the latency of N2.

Although the Klinke et al. report appeared in 1968, P3 continued to hold center stage in theories concerning target selection and related processes, presumably because it was not clear that P3 latency was too long to reflect those processes. When the importance of N2 became clear because of RT data, it was hypothesized that N2 and P3 were both components of a complex waveform emanating from the same brain tissue. Topographic analyses of ERP associated with omitted stimuli (Simpson et al. 1976), however, showed that N2 and P3 had different intracranial sources. Furthermore, N2 was modality-specific in its distribution, whereas P3 was not.

Similar results were obtained in a vigilance experiment in which the targets consisted of random changes in physical parameters (Simson et al. 1977). The modality specificity of N2 suggested that different neural ensembles accomplish auditory and visual discriminations. The circumstance that N2 preceded P3 in latency for ERPs elicited by stimulus omission indicated that N2 reflected the detection of omitted stimuli and P3 some other process. Results of the vigilance study suggested that N2 reflected target selection whether the target was an omitted stimulus or a change in parameter of a physically present stimulus. These results are detailed elsewhere (Ritter, this volume).

As pointed out earlier P3 is the only component with a range in latency hitherto known to be great enough to be related to RT. If N2 reflects target selection or related processes, then N2 latency should vary as a function of the difficulty of target selection and correlate with RT. Recently completed data analysis supports that conclusion (Ritter et al., in preparation). Reanalysis of the data of Ritter et al. (1972) indicates that, in single-trial measurements of N2 elicited by the targets of the vigilance task, the mean latency of N2 increased across conditions as a function of the difficulty of the discrimination of the targets within conditions. Furthermore, the single-trial analysis yielded somewhat greater product-moment correlations within conditions between N2 and RT than was previously found between P3 and RT.

On the basis of these considerations, it seems appropriate to propose that the earlier hypotheses relating P3 to information delivery, target selection, and related processes be shifted from P3 to N2. In this case, the only relevant hypotheses concerning the functional significance of the physiological activity underlying P3 would be those associated with preparation for future events. Since there are no published studies of these alternative possibilities, there is a clear need for experiments that examine new hypotheses concerning the functional significance of P3.

Hillyard (personal communication) has raised the possibility that, although P3 is too late to directly reflect target selection, it might nevertheless indirectly reflect selection by virtue of a delay between critical neural activity and the manifestation of P3 at the scalp. Somjen (this volume) indeed mentions the possibility that some late components could be due to glial potentials (with a delay of as much as 100 msec between neural activity and the detection of a glial potential at the scalp). Thus, Hillyard (personal communication) points out: "Suppose, for instance, that the P3 was generated by the depolarization of glial cells consequent upon the release of K + ions by the active neurons which do the selecting. The delay between the neural activity and its direct glial 'reflection' could account for the delay of P3 *re* the selective response."

Although this possibility must be considered, it opens a Pandora's box. At present neural and glial potentials at the scalp cannot be distinguished, except for early potentials with a latency presumably too short to reflect glial potentials. The sequence with which the neural activity associated with various late potentials would thus be unknown. Imagine, for example, that either P2 or N2 (or both) reflect neural activity directly and P3 reflects glial potentials generated by neural activity that precedes the neural activity of either P2 or N2 (or both). Some glial potentials might be associated with a delay of 50 msec and others with 100 msec or values in between. Thus, the neural activity of P2, N2, and P3 could occur in any sequence imaginable, including the possibility of their simultaneous occurrence. In view of the havoc these possibilities entail, and the variety of *post hoc* speculations open to the whim of a given investigator's theoretical inclinations, the following is suggested: until it is established empirically that scalp-recorded ERP components can reflect glial potentials, all ERP components (with the possible exception of dc potentials) should be considered to be directly related to neural activity and, therefore, the latency of a component should indicate the time of occurrence of the neural events that produce that component. These assumptions appear to provide the most parsimonious framework currently available for the interpretation of ERPs.

EQUIVOCATION AND P300 AMPLITUDE

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The purpose of this paper is to briefly review evidence for the concept that the information *received* by a subject from the occurrence of an event determines, in part, the amplitude of the P300 component elicited by the event. We do not mean to imply, however, that other variables are not also relevant in determining P300 amplitude or that the P300 wave is a unitary phenomenon.

Review

In the framework of classical information theory (Shannon and Weaver 1949), the amount of information *provided* by an event is related to the subject's *a priori* uncertainty of the event's occurrence; the lower the *a priori* probability of occurrence, the greater the information provided. However, the amount of information *received* by the subject equals the information provided by the event minus an information loss related to the subject's *a posteriori* uncertainty of having correctly perceived the event; the greater the *a posteriori* uncertainty, the greater the information loss. In information theory terms, this loss is referred to as *equivocation*.

The role of *a priori* event probability was explicitly recognized in the initial investigations of P300 (Sutton et al. 1965). Sutton et al., Tueting et al. (1970), Friedman et al. 1973), and Ruchkin et al. (1975) have used a paradigm in which the subject guessed what the ensuing stimulus would be. When stimulus probability was manipulated, P300 amplitude varied inversely with the joint probabilities of the stimulus and guess (outcome probability). Donchin et al. (1973) modified this procedure by varying the complexity of the sequence in which stimuli were presented. P300s were smallest when simple, easily predictable sequences were used and became progressively larger as the sequences became more complex and thereby more difficult to predict. Karlin and Martz (1973) investigated the P300 component in choice-reaction time and delayed-choice paradigms. They reported that stimulus and response probability jointly influenced P300 amplitude, with the least probable combination eliciting the largest P300. Paul and Sutton (1972) and Squires et al. (1975b) varied the probability of occurrence of the signal in auditory signal detection experiments. The P300 elicited by detected signals was largest when signal probability was lowest.

Squires et al. (1973) used a paradigm in which the subject performed an auditory intensity discrimination. In each trial, the subject indicated the degree of confidence in his decision. This was followed by a visual stimulus that gave feedback on accuracy. It was found that when the stimulus confirmed a high-confidence decision, P300 was smallest. When the stimulus disconfirmed a high-confidence decision, P300 was largest.

A common element of the experiments described above is that the stimulus provided information that resolved the subject's uncertainty with respect to a prior expectation. As the subject's estimate of the *a priori* probability of the occurrence of an event decreased, the amplitude of the P300 elicited by that event increased. To the extent that the information content of an event may be viewed as being inversely proportional to its *a priori* probability, the amplitude of P300 can be interpreted as reflecting, in part, the amount of information provided by the event.

There also have been several reports of the effect upon P300 amplitude of the subject's *a posteriori* uncertainity of perception. Mast and Watson (1968), Hillyard et al. (1971), Paul and Sutton (1972), and Squires et al. (1975b) have investigated the behavior of P300s elicited by auditory stimuli near sensory threshold. Mast and Watson utilized a signal-counting procedure. Their results suggested that P300 amplitude was related to the subject's criterion for detecting presence of a signal. Hillyard et al, Paul and Sutton, and Squires et al. utilized standard signal-detection paradigms (Green and Swets 1966). Hillyard et al. (1971) investigated the relationship between discriminability (d′) and P300 amplitude. They reported that P300 increased as discriminability increased, up to a level of about 90% correct responses. Paul and Sutton (1972) used a fixed stimulus intensity and varied the subject's criterion by manipulating pay-off contingencies. P300 amplitude elicited by correct detections increased as the criterion became more strict. Squires et al. (1975b) also used a fixed stimulus intensity. Their subjects responded with a numeric confidence rating. P300 amplitude was largest when the subject was most confident of his decision.

The common finding of these investigations is that P300 amplitude increased as the subjects were more certain of their perceptions and hence the information loss due to equivocation was less. Hillyard et al. demonstrated this by direct variation of discriminability of the stimulus, while Paul and Sutton in effect varied the degree of certainty required of the subjects, and Squires et al. segregated the data into different levels of certainty. Donchin (1968) reported similar findings in a visual perception experiment involving threshold flashes. P300s were large when the subjects were certain of their judgments and small when the subjects were uncertain.

Further evidence for the role of equivocation in determination of P300 amplitudes is provided by discrimination experiments reported by Ritter et al. (1972), Adams and Benson (1973), Lang et al. (1975), and Ford et al. (1976). Ritter et al. investigated the relationship between P300 latency, reaction time, and auditory pitch discrimination in a go-no go paradigm. Two conditions were used. In one, the discrimination was relatively easy; in the other, it was difficult. While the authors did not specifically report the effect of discrimination difficulty upon P300 amplitude, inspection of their published waveforms indicates that P300 amplitude was lower when the discrimination was more difficult. Lang et al. (1975) instructed subjects to rank five different equi-intensity tones. The tones, presented individually, were 700, 1000, 1100, 1200, and 1500 Hz. There were relatively few errors for the 700- and 1500-Hz tones, while errors were relatively numerous for the 1000-, 1100-, and 1200-Hz tones. Peak-to-peak amplitude from N100 to P300 was significantly larger for easily ranked tones than for tones that were difficult to rank.

Adams and Benson (1973) used a relatively high-intensity (30 dB SL) auditory stimulus to signal correct performance of a difficult psychophysical task. Incorrect performance was indicated by presentation of a lower intensity stimulus. Objective intensity contrast between the two alternative stimuli was manipulated by varying the intensity of the stimulus that indicated incorrect performance (from 0 to 24 dB). As the contrast was reduced, amplitude of the P300 elicited by the fixed-intensity stimulus was reduced, although the stimulus provided the same *a priori* information. Increased equivocation as stimulus contrast decreased is a parsimonious explanation of this finding. However, Adams and Benson did comment that subjects were able to readily distinguish between the two stimuli, although the investigators did not determine whether there were any objective differences in the ease with which the distinction could be made. The fact that the subjects apparently readily distinguished between two stimuli does not necessarily vitiate the equivocation argument.

Thurmond and Alluisi (1963) demonstrated, in a choice-reaction time experiment, that as dissimilarity between two signals was reduced, reaction time increased, even though discriminability remained high. This indicates that although a relatively small degree of equivocation may not significantly interfere with the ultimate accuracy of a decision, it will delay it, due to increased difficulty in processing the signal.

Ford et al. (1976) have provided further support for this interpretation. They presented subjects with a sequence of tone pips at a fixed loudness level and frequency. Occasional mismatch tone pips were presented on a random basis, there being three levels of frequency mismatch: (1) a 5% frequency shift (2) a 25% shift, (3) an octave shift. Subjects were required to respond to the mismatch tones with a button press. P300s elicited by the mismatch tones increased in amplitude and reaction time decreased as the degree of mismatch increased, despite the fact that subjects responded correctly to 89% of the 5%-frequency-shift trials and to 96% of both the 25%-shift and octave-shift trials. Ford et al.'s results provide a further demonstration of the effect of equivocation upon P300 amplitude. Their results also directly demonstrate that P300 amplitude may reflect the degree of difficulty in reaching a decision rather than the final accuracy of the decision-making process, as indicated by the accuracy (which did not vary), reaction time (which increased), and P300 amplitude (which decreased) for the octave and 25%-shift conditions.

Reduction in average P300 amplitude with increased equivocation may be due to a direct decrease in amplitudes in individual trials and/or to increased latency variation of P300 in individual trials. The latter possibility seems particularly likely if one assumes that equivocation leads to variability in decision time and that P300 latency is linked to the time at which a decision is made.

An opportunity to examine these alternatives was afforded by investigations of the emitted potential. An emitted P300 may be elicited by the nonoccurrence of a relevant stimulus that may or may not occur at a given point in time. Emitted P300s have been observed in guessing experiments (Sutton et al. 1967, Ruchkin and Sutton 1973) and some signal detection experiments (Squires et al. 1975b). Average emitted P300s in guessing experiments are smaller than corresponding evoked P300s elicited by stimulus occurrences. Ruchkin and Sutton (in press) demonstrated that the lower average amplitude was due partly to increased latency variation of emitted P300s and partly to a direct amplitude difference. The direct amplitude decrement as well as the increased latency variability may be due to temporal uncertainty and hence increased equivocation associated with identification of the nonoccurrence of a stimulus. There have been several reports of the occurrence of clear evoked P300s in correct detection trials of signal-detection experiments, but the evidence for the occurrence of emitted P300s in signal-absent trials is more limited. Hillyard et al. (1971) and Paul and Sutton (1972) were unable to observe emitted P300s. Squires et al. (1975b) reduced temporal uncertainty through the use of a cue light and sorted their data into high and low decision-confidence trials. They observed emitted P300s in high-confidence correct rejection and false-alarm trials. They further demonstrated that emitted P300 amplitude in correct rejection trials increased as stimulus intensity increased. Squires et al.'s results suggest that latency variations may in part contribute to the lower amplitudes of average emitted P300s. However, the effect of decision confidence and stimulus intensity upon emitted potentials in signal-absent trials suggests that equivocation also has a direct effect upon P300 amplitude.

The results of the investigations cited in this paper can be most parsimoniously described as follows: P300 amplitude is in part determined by the total amount of information received, i.e., the greater the reduction in uncertainty, the greater the P300. P300 can vary as a function of information received in two ways: (1) for a fixed level of prior uncertainty, P300 amplitude will be determined by equivocation–decreasing as equivocation increases; (2) for a fixed level of stimulus equivocation, P300 amplitude will be determined by prior uncertainty–increasing as uncertainty increases. The latter relationship is subject to the provision that equivocation is not so large that *a priori* probability effects are "swamped" by the high degree of *a posteriori* uncertainty (Squires et al., 1975 b). What seems to be at issue in the former relationship is not necessarily outright discriminability or correctness, but the immediacy and ease with which a decision can be made. This suggests that P300 amplitude may reflect processes involved in the early stages of decision making rather than the final, conscious step.

Summary

Evidence for the concept that the amount of information received by a subject from the occurrence of an event determines, in part, the amplitude of P300 is reviewed. The amount of information received depends upon the *a priori* uncertainty of the event's occurrence minus an information loss, referred to as equivocation, due to the *a posteriori* uncertainty of having correctly perceived the event. Support for this concept is provided by the results of experiments in which either or both *a priori* probability and equivocation were variables.

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THE LATE POSITIVE COMPONENT AND ORIENTING BEHAVIOR

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Review

The concept of orienting is an old one, dating back to the work of Pavlov, who noted (at first, in annoyance) that his experimental animals directed their attention to any novel or unusual stimulus in the experimental chamber. He thus termed it the "investigatory" or "what is it?" response. The orienting response consists of a series of physiological changes including heart-rate deceleration (Graham and Clifton 1966), pupillary dilation (Shakhnovich 1965), increments in galvanic skin response (GSR) (Lovibond 1969) and EEG desynchronization (Lynn 1966). It has been shown to be elicited by such stimulus characteristics as novelty and uncertainty (see Lynn 1966), some of which have also been shown to influence the ubiquitious P300 wave. The orienting response has received much experimental attention with the use of electrodermal variables, heart rate, and pupillary dilation, but it is only within the last decade that the late positive component has been added to the list of "components of the orienting response."

Ritter et al. (1968) were the first to use the classical orienting response paradigm to elicit averaged evoked-potential components of this response. They presented a series of 1000-Hz tones at 2-sec intervals. There were 30 stimuli per run and 24 runs. In order to look at habituation within the stimulus train, Ritter et al. averaged by stimulus position within the train, across the 24 runs. A substantial decrement in P200 was observed as a function of stimulus position, but in a second experiment where stimulus presentation was changed to one every 10 sec, no decrement in P200 was seen, so that refractoriness (Davis et al. 1966) and not habituation seemed to be the cause of the decrement. In a third experiment, 1000-Hz tones, one every 2 sec, were delivered with a pitch change to 2000 Hz at the 21st stimulus. Stimulus position averaging revealed a short-term decrement in P200, but the pitch change did not restore the amplitude of P200. The change in stimulus quality produced a change in the evoked-potential waveform, with a parietal-maximum, late positive component at 350 msec. In a fourth experiment, the paradigm was changed to include the unpredictable onset of a run (temporal uncertainty) and an unpredictable pitch change within a run. Both of these unpredictable changes produced parietal-maximum late positive components at 350 msec. Thus, Ritter et al. (1968) demonstrated that P300s were elicited in situations identical to those used to elicit autonomic components of the orienting response.

Support for P300 as a component of the orienting response could be strengthened by concomitant recording of autonomic measures. Evidence from a variety of laboratories had indicated that heart rate (Higgins 1969), GSR (Lovibond 1969), and pupillary dilation (Levine and Hakerem 1969) were similarly affected by manipulations of stimulus uncertainty, one of the early postulated psychological correlates of P300. Tueting et al. (1970) had shown that P300 varied markedly in amplitude with changes in stimulus probability in an uncertainty paradigm. We (Friedman et al. 1973) followed these lines of evidence by recording both evoked potentials and pupillary dilations in a modification of the Tueting et al. (1970) probability paradigm. Pupillary dilation is easily time-locked, with an approximate 1-sec latency to peak and, when averaged, can be distinguished from noise with approximately the same N as P300 (Hakerem 1967). We found that pupillary dilation followed the same lawful relationship to probability of occurrence as did P300: the lower the probability, the larger the amplitude of dilation. In addition, a component of the dilation response, prestimulus slope, followed a similar time course and was closely related to CNV amplitude, tending toward dilation when subjects were guessing upcoming events (CNVs were more negative) and toward constriction (CNVs were less negative and some were positive) when they were told which stimulus would occur next (Friedman 1972). This paradigm was not the traditional "orienting" paradigm. In informational terms, however, both P300 and pupillary dilation were larger in amplitude when an infrequent event reduced uncertainty. The concept of uncertainty reduction has been used before within an orienting framework (Pribram 1967, Sokolow 1960).

Roth et al. (this section) recorded GSR and evoked potentials in an orienting response paradigm where chords unpredictably and continuously (unlike the Ritter et al. 1968 paradigm) replaced background noise bursts. They used GSR as a criterion measure for sorting P300s to the chords into high- and low-amplitude averages. During attend conditions (respond to the change), GSR and P300 showed similar amplitude changes. During read (i.e., ignore) conditions, there was a dissociation of the two measure, with small-amplitude P300s associated with large-amplitude GSRs. Roth et al. (1976) speculated that direction of attention affected P300 and GSR differently, with a larger GSR orienting response when attention is *not* directed towards the stimulus train. This result holds only for the "read" condition.

In both the Tueting et al. (1970) and Friedman et al. (1973) "certain" conditions (subjects told what stimulus to expect), P300 amplitude was still a monotonic function of stimulus probability even though stimuli were "task-irrelevant." Roth (1973) and Roth and Kopell (1973) also demonstrated that infrequent, task-irrelevant stimuli produced reliable P300s, but in the case of Roth's investigation (1973), P300s were of much earlier latency (mean of 210 msec) than previously reported. In further support of this "early P300" as an orienting potential, these investigators found a decrement in amplitude across quarters of the experimental run. Response decrement is to be expected as the novelty of a repeated change in stimulation diminishes. Habituation of the orienting response with repetition is one of the key postulates of orienting response theorists (Lynn 1966).

Theoretically, an orienting response is expected whenever background stimulation (to which subjects are assumed to habituate) is changed in any manner—hence, the use of prolonged runs of standard stimuli with infrequent changes. The finding that P300s were present for task-irrelevant, nonattended stimuli (Ritter et al. 1968, Roth 1973) as well as for attended, task-relevant stimuli (Ritter et al. 1972) poses a problem for any unified theoretical interpretation of the P300 wave. On the other hand, if there are two P300s, one elicited when variables that produce orienting are used and the other when task-relevance is the key feature of the experimental design, then interpretation is easier.

Squires et al. (1975) distinguished the "orienting" from the "attend" P300 by both latency and scalp topography. They utilized a paradigm in which subjects either attended or ignored infrequent background stimuli and infrequent intensity or pitch changes. During the attend condition, subjects counted changes and during the ignore condition, they read. The ignore condition produced P300s only to the lowest probability stimuli ($p = 0.10$). This P300 varied in latency from 220 to 280 msec (similar to that of Roth 1973), and had a frontocentral topographic distribution. When subjects attended, this "P3a" wave was present but was overridden by a later (310-380 msec), more posteriorly distributed "P3b" wave. Squires et al. (1975) concluded that the presence of the "P3a" wave reflected a "mismatch to an ongoing stimulus train, whether or not it is being attended" (p. 399). This conclusion is in accord with Sokolov's (1960) theoretical model, which postulates that any changes in background stimulus conditions leads to a mismatch with the neuronal model and results in an orienting response.

Courchesne et al. (1975) studied the influence of novelty on the late positive component of the visual evoked potential, using easily recognizable and completely unrecognizable novel stimuli. Novel stimuli were interspersed (each with 5% probability of occurrence) among frequent nontarget stimuli (the number 2) and infrequent task-relevant target stimuli (the number 4). The subject had to count the target stimuli, which occurred with 10% probability. Evoked potentials for the counted 4s and the task-irrelevant, completely unrecognizable novel stimuli contained late positive components that differed in scalp topography, but not in latency. Novel stimuli produced a more anteriorly oriented distribution, while the counted 4s produced a more posterior scalp topography. When evoked potentials elicited by the first, second, and third presentations of these novel stimuli were averaged separately, there was a large decrement (50% for the second stimulus) in P300 amplitude, thus demonstrating habituation of the response and supporting an "orienting" interpretation of this frontally distributed wave.

The more frontal distribution of the potential for novel visual stimuli reported by Courchesne et al. (1975) supports the data of Squires et al. (1975) for the auditory modality, but differences in latency and task mitigate against an association between the auditory "P3a" wave and the late P3 to novel visual stimuli. It is possible, however, that the two waves are part of the same orienting potential, but differ in latency and amplitude, depending upon stimuli and task conditions. This latter possibility may well be in accord with another of Sokolov's postulates that the amplitude of the response varies with the degree of mismatch from the neuronal model. For example, Sokolovian theory would predict a larger amplitude response to a more novel visual stimulus (Courchesne et al. 1975) than to a less novel pitch change (Squires et al. 1975). Comparision of these two studies, in fact, confirms this prediction: P300s to unrecognizable novel stimuli (Courchesne et al.) were larger in amplitude than P300s to easily recognizable novel stimuli (Squires et al.).

This latter postulate was directly tested by Ford et al. (1976), who parametrically varied the degree of disparity of infrequent pitch changes from standard, frequent background tones. Mismatch tones were 5% (one-half musical step), 25% (major third), and 100% (an octave) discrepant and were interspersed during read (ignore) and respond (button press to mismatch) conditions. Under both read and respond conditions, the amplitude of P300 varied with the degree of mismatch, although this relationship was much clearer and stronger under respond conditions. P300 latency was longer during respond (mean of 336 msec) than during read (mean of 287 msec), and the topographies were different as well. The read P300 was more uniformly distributed, while the respond P300 was largest at Pz. These data support an interpretation of P300 in terms of orienting dependent upon the degree of mismatch and support the hypothesis that more than one P300 generator exists, producing P300s of different latency and amplitude.

Summary and conclusions

Enough evidence has accrued to suggest that P300 does reflect orienting, since it is elicited in the same situations and by the same variables that elicit the classical autonomic components of the orienting response. The fact that late positive components of different latencies and scalp topographies have been elicited under similar orienting paradigms presents a problem in attempting to draw general conclusions about situations that produce an "orienting P300." In general, early and more frontally distributed late positive components have been reported to occur when subjects were ignoring the stimuli, while longer latency late positive components have been found when they were attending the train of stimuli, even though the stimuli were task-irrelevant (i.e. Courchesne et al. 1975). Ritter et al. (1968) found a late (350 msec) P300 that had a posterior focus, while Squires et al. (1975) reported an early (220-280 msec), frontally distributed "P3a" and Ford et al. (1976) observed an early (287 msec), but more uniformly distributed P300 to auditory stimuli during "ignore" conditions. It has been suggested by Roth (1973) and Squires et al. (1975) that the late P300s reported by Ritter et al. (1968) were "target-detect" P300s, since their subjects were practiced and were expecting the pitch change, thus accounting for the longer latency and posterior topography.

In any event, it is likely that one of the various P300 waves will occur when experimental operations designed to induce orienting behavior are employed. The conditions, stimuli, and tasks under which the production of these waves can be wholly attributed to orienting remain to be parametrically investigated. The addition of autonomic measures to these same paradigms might aid in the interpretation of orienting, and use of single-trial analysis (Ritter et al. 1972, Courchesne et al. 1975), especially in the case of large amplitude autonomic signals (e.g., GSR), might provide information that is "washed out" when the technique of averaging is used.

DOES P300 REFLECT TEMPLATE MATCH/MISMATCH?

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The mentalistic concept of template matching has been used by psychologists to explain pattern recognition. When used by psychologists, template means a standard or a prototype. A stimulus is identified by noting its congruence with the template (Neisser 1967). Although the concept has some appeal at first blush, it loses strength when it becomes apparent that in order to explain much of perception, it is necessary to make the definition much more flexible, ultimately making template-matching theories indistinguishable from feature-analysis theories. For example, if the task is to detect any letter A, then the template will be a composite of block A's, script A's, tilted A's, etc. Regardless of these definitional problems, evoked potential researchers often think in terms of templates to explain the P300 phenomenon. To do this, a flexible notion of how a match or mismatch is made is adopted. The template is some kind of memory of stimulus events. New stimuli are compared with this template, and a match or mismatch occurs. Depending on task or environmental demands, the template will be more or less fuzzy.

A number of variables affect P300. Two of them, task relevance and probability, are discussed in this paper. Since these variables interact in a complex manner, studies in which only one is manipulated, the other being held constant, are considered. The success or failure of template matching and mismatching in explaining existing P300 data is examined, after first defining template matching and mismatching in terms of task relevance and probability.

Definitions

Task-relevant stimuli are stimuli that a subject needs to make a decision. They are either stimuli requiring a response (a target) or stimuli having some bearing on the decision regarding the target, perhaps affecting performance. In experiments where the subject is instructed to detect a particular signal, some researchers assume the subject learns what the target is and develops a template (neural representation) of it in memory. When a signal occurs that matches the template, the subject decides that the target has occurred. This template will be referred to as the target template. It has been suggested that it is a match of the sensory input with the target template that elicits the P300.

Probability has also been shown to affect P300 amplitude. P300 amplitude has been manipulated by varying the probability of ongoing events, either the global or the sequential probability, or by varying the outcome probability. These events are psychological events manipulated by the contingencies between physical events. Templates of these events may be the environmental templates of Sokolov (1963). To determine the effect of any type of probability on P300, it is important to establish that both the probable and improbable events are task relevant and equally discriminable. In experiments where the subject grows accustomed to hearing or seeing a certain background signal or experiencing a certain event, some researchers assume that the subject develops a template for the probable event. When another event of a different pitch, configuration, or psychological value occurs, the input mismatches his template. This template will be referred to as a probability template; and when the observed event mismatches the probable event, a P300 results. The probable stimulus could be considered a probability template match; and unless it is also task relevant, it does not elicit a large P300 (Squires et al. 1975). Expectancy is a term often used interchangeably with probability. Since the subject is rarely asked what he really expects in these experiments, it is better to use the more operational term of probability.

Target template matching

The most direct attack on the issue of target matching was made by Posner et al. (1973). The experiment was a match-to-target design where subjects were shown a target letter followed 1 sec later by another letter. The second letter either matched or mismatched the target. A match elicited an earlier and larger P300 than did a mismatch, but the mismatch elicited a larger N2 than did the match. Matches often have faster (Posner and Boies 1971) and less variable (Nickerson 1969) reaction times (RTs) than do mismatches. The psychological process underlying this phenomenon is unclear. Nevertheless, inferring from RT data, it seems reasonable that P300s to mismatches would be later and the onset of individual P300s would be more variable. These factors could explain the late, shallow appearance of P300 to mismatches, and had they been averaged with respect to RT (keeping RT and RT variability equal for both matches and mismatches), the P300s might have looked quite similar. However, since the difference between standard deviations in RT is usually less than 25 msec (Sternberg 1969), it is unlikely that this could explain the difference in broadness of P300 seen in Posner's data.

Another example of target matching and mismatching, when matches and mismatches were equiprobable, is an experiment by Courchesne et al. 1976. Seven subjects saw 80% background slides (2's), 10% targets (4's), and 10% novels (colorful, unrecognizable pictures). Subjects were required to count the targets. For the moment, assume that the subject has a template for the target so that its delivery results in a match and the delivery of a novel results in a mismatch. The match evoked a large parietal P300 and the mismatch evoked a large frontal-central P300 (and N2). In another condition, where subjects counted the novel slides, the novel stimuli evoked a large parietal P300, as did the target 4's in the other condition. Since no novel slide was ever presented more than once, it is difficult to imagine a template of a particular novel slide. In order to make these data fit the notion of template matching, we must think of a general template for any complex stimulus (Tueting, this volume).

The relationship between target template-matching and P300 has been studied extensively by the Hillyard/Squires group (Hillyard et al. 1971; Squires et al. 1973a, 1973b, 1975). On the basis of signal detection experiments, these authors suggest that subjects establish two templates in memory—one for signal presence (a template of the signal itself) and one for signal absence. P300 is triggered by a match to either template, and the closeness of the match is measured by decision confidence. The closer the match, the larger and earlier the P300 (Squires et al. 1973b). One interesting result in the 1975 study was that detections of signal presence (hits) are associated with larger P300s than are detections of signal absence (correct rejections) made at the same level of confidence. To explain this result, a second variable, related to stimulus probability, was suggested and tested. This variable was the outcome probability of a trial. The more improbable the outcome, the larger the P300. That is, when signal absence is improbable, correct rejections also become improbable and evoke larger P300s than do correct detections. Squires et al. 1975 pointed out that, when a signal is well above threshold, when subjects are confident that a signal has been delivered, and when task relevance is not varied, improbability of outcome seems to play a more dominant role than target template-matching.

Probability template mismatch

Throughout the literature, P300s evoked by improbable events are reported. In two separate experiments, Tueting et al. (1970) varied the sequential and global probabilities of stimulus occurrence. When subjects were asked to guess which of two stimuli would occur next, Tueting et al. found that P300 amplitude was predicted by the interaction of the stimulus probabilities and the guessing behavior of the subject. The interaction was called the outcome probability; the more improbable the outcome, the larger the P300.

K. Squires et al. (1976) also investigated the effect of both sequential and global probability on the ERP waveform. Instead of probability, they called the variable *expectancy.* Expectancy was defined as a mathematical function of decaying memory for events within the prior sequence. For target stimuli, P300 (as well as N200 and slow wave components) varied inversely with stimulus expectancy.

An improbable event can also be response-related. Karlin and Martz (1973) have shown that, when a response is rare, the stimulus associated with the response elicits a larger P300 than when the response is frequent regardless of stimulus probabilities.

When improbable feedback is delivered, a large P300 is elicited (Squires et al. 1973a, 1975; Tueting et al. 1970); when an infrequent pitch or intensity change occurs, large P300s are elicited (Ritter et al. 1968, Ford et al. 1976, Squires et al. 1975); when an infrequent line drawing occurs in a series of letters, a P300 is elicited (Courchesne et al. 1975); and so on. Thus, it appears that improbable events associated with stimulus, response, or outcome evoked larger amplitude P300s. Many reports can be reinterpreted in terms of a mismatch with the probability template eliciting a P300, although few investigators have used these terms.

In summary, the largest P300s are elicited in two fairly disparate situations—target template matching and probability template mismatching. To reconcile this disparity may not be possible within the framework of template matching and mismatching, but some of the possible ways are suggested below.

Tueting (this section) suggests that target template-matching and probability template-mismatching might be pulled together under a unitary concept by assuming, in the probability case, that the subject establishes a template for improbable or novel events. Another speculation is that the two processes can be considered component parts of a serial process where probability mismatches are registered first, followed by an evaluation of whether the event matches the template. When an event mismatches the expectancy, an early P300 should result; when it matches a target, a later P300 should result. This concept fits the data of N. Squires et al. (1975) and Roth et al. (1976), but is inconsistent with the data of E. Courchesne et al. (1978) showing that probability mismatches elicit later P300s than do targets in the visual system. Roth et al. (in preparation) have obtained similar inconsistent data in the auditory system. Furthermore, this concept does not deal with the occurrence of target mismatches as in Posner's work (1973), or with how P300 amplitude and latency might change with the degree of match or mismatch.

Squires et al. (1975) formulated a way in which P300 could be affected by the degree of target matching. They suggested that template matching may involve a series of comparisons of the signal against a list of templates that vary from the most target-like to the least target-like. P300 would be elicited when a match is satisfactorily encountered, causing P300 latency variations. The confidence in the decision that a match actually occurred would be reflected in P300 amplitude. The same logic can presumably be extended to the probability situation, in which the list of templates is ordered from the most expected to the least expected. N. Squires et al. (1975), however, adopted a different strategy. Instead of trying to unite target matching and probability mismatching under one rubric, they suggested that the P300s elicited under these two situations are separate components (P3b and P3a) that have different latencies and scalp distributions and reflect different processes. P300 data at the present time do not permit the unequivocal evaluation of the different template match-mismatch hypotheses discussed in this paper.

EVOKED POTENTIALS AND FEEDBACK[1]

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More than 10 years ago, Sutton et al. (1965) reported that subjects had larger P300s on discovering that a guess was wrong than on discovering it was right. However, in subsequent experiments, this pattern was noted to be inconsistent. In some experiments, no statistical difference was found. In one experiment, most subjects had larger P300s associated with feedback that informed them their guess was right (Levit et al. 1973).

On noting how sensitive P300 amplitude was to the interaction of stimulus and guessing probabilities (guessing probabilities were not examined in the earlier experiments), the assertion that being wrong gave greater amplitude than being right was temporarily withdrawn, and it was suggested that the issue of right-wrong differences could not be resolved until it was disentangled from the effects of probability (Tueting et al. 1970). At about this time, Squires et al. (1973) looked at feedback that told a subject that his discrimination was correct or incorrect, and found that P300 was larger when feedback indicated an incorrect discrimination. These differences remained even after probability effects were statistically partialled out. Poon et al. (1974) used a guessing procedure in which subjects could learn the correct sequence of stimuli to a fairly high degree of accuracy. Again, they found that P300 was larger for incorrect than correct feedback.

In contrast to studies reporting larger P300s for incorrect feedback, a recent study by Leifer et al. (1976), also a guessing situation, found larger P300s associated with correct feedback. But an inkling of the complexity of the problem is given by their analysis of changes over successive blocks. P300s associated with feedback following predictions that the high probability event would occur became smaller in amplitude over successive blocks. However, P300s associated with feedback following predictions that the low probability event would occur did not alter over successive blocks. On the other hand, in a simpler 50-50 probability situation not involving probability learning, Tueting and Levit (unpublished data) found that incorrect guesses had larger P300s at the beginning of the experiment, but this reversed as the experiment progressed so that correct guesses had larger P300s in later trials.

More recently, we attempted a reanalysis of the feedback concept and have completed some preliminary experiments based on that reanalysis. We developed the following formulation: Whether stimuli provide feedback with respect to a guess or with respect to a discrimination, they have the following cross-cutting properties:

1. Confirmation-disconfirmation – The feedback stimulus tells the subject that a guess or discrimination was correct or incorrect.
2. Degree of value–This can be illustrated by experimental designs in which the experimenter places different degrees of monetary reward or loss on being correct or incorrect.
3. Direction of value–We are used to thinking of being right as a good thing and being wrong as a bad thing. But it is not always so, as illustrated in the statement, "Damn it! I knew it was going to rain!" or when one is sure that some symptom means cancer and then discovers that it indicates only a minor ailment.
4. Information–A feedback stimulus delivers information relevant to future guesses or judgments (e.g., it may indicate that the last judgment was wrong, and that the subject should try to find some other basis for the next response). We have, however, generally only assumed that feedback influences the subject's guessing and discrimination strategies on future trials and that these changes are reflected in P300. A somewhat different approach is to construct

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experimental designs in which one controls the information provided by the feedback stimulus in order to study more directly the degree to which it affects the subject's behavior and evoked potentials on future trials. An interesting experimental design is one arranged so that the subject's being correct or incorrect on a given trial is used by the experimenter to determine the subsequent probability with which different stimuli will be presented.

In a recent set of experiments, we attempted to disentangle two of these properties of feedback, confirmation-disconfirmation and direction of value. The direction of value concept is more familiarly known as the win-lose dimension.

In one experiment, 12 subjects guessed in each trial whether the next stimulus would be a high-pitched click or a low-pitched click. Thus, in each trial, as the click occurred, the subject discovered whether the guess was correct or incorrect. This single outcome, however, did not determine whether the subject won or lost. The subject had been instructed that winning or losing was based on performance in each pair of trials, according to the following rules: the subject won a quarter if both members of the pair were right or if both members of the pair were wrong. The subject lost a quarter if one member of the pair was right and the other was wrong. Note several things about this design. Being right on the first member of the pair did not in itself determine the payoff. If the second was also right, the subject won; if the second was wrong, the subject lost. Likewise, being wrong on the first member of the pair did not determine payoff. If the second was also wrong, the subject won; if the second was right the subject lost. Furthermore, with respect to the second member of the pair, the subject could win on right or on wrong guesses or could lose on right or on wrong guesses. Thus we experimentally separated confirmation-disconfirmation from winning and losing. (With some subjects, we played the game with opposite rules.)

The overwhelming finding was that P300 to the second member of the pair was much larger than to the first member of the pair, as shown in Fig. 1. This difference in amplitude might be attributed to the fact that the response to the second stimulus involved completion of the pair; however, related data suggest that this was not the basis for the finding. Another interpretation is that the larger P300 for win-lose reflects a value dimension that is often forgotten in formulations with respect to P300; winning or losing a quarter is more important than simply having a guess confirmed or disconfirmed.

Other findings were less dramatic. For the second member of the pair, P300 was usually larger and later for lose than win. A more general finding was greater

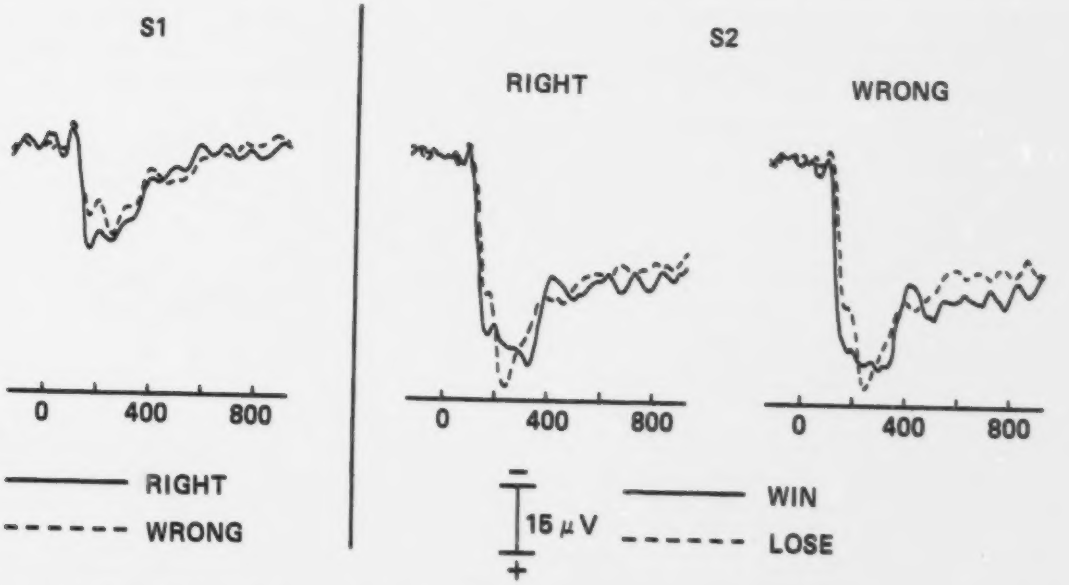

Fig. 1. Vertex auditory evoked potentials for one subject in a guessing paradigm. Negative at vertix is up with respect to a linked earlobe reference. The first stimulus of the pair (S1) confirmed or disconfirmed the subject's guess. The second stimulus of the pair (S1) also confirmed or disconfirmed the subject's guess, but the subject won or lost money depending upon the joint outcome of the guesses preceeding S1 and S2 and S1 and S2 were separated by a minimum period of 5 seconds.

negativity in the P2-N2 region for the lose waveform for the overwhelming majority of subjects. On the whole, these differences between lose and win waveforms held whether they occurred in experimental formats where the subject lost by being wrong or lost by being right and correspondingly won by being right or won by being wrong. This is the direction of value concept mentioned earlier. Identification of more subtle interactions must wait until all data have been retrieved from the computer. Data for all scalp loci also have not been fully examined; only vertex has been analyzed at this time.

In the confirmation-disconfirmation waveforms—responses to the first member of the pair—consistent differences were again in the P2-N2 region. The disconfirmation waveform, for almost all subjects, was more negative in the P2-N2 region. Unlike the win-lose comparison, there were no differences in the P300 region.

Summarizing, then, in feedback designs the P300 is very sensitive to the importance or value of the stimulus to the subject, as reflected by the fact that win-lose P300s were much larger than confirmation-disconfirmation P300s. On the other hand, differences between winning and losing, as well as between confirmation and disconfirmation, were reflected most consistently in the P2-N2 region.

In the correspondence group discussion, preceding this symposium, Squires reexamined earlier data from Squires et al. (1973), which compared confirming and disconfirming feedback in a discrimination situation. The earlier data appear remarkably similar to ours. The statement that there was more negativity in the P2-N2 region summarizes what was most consistent over all of our subjects. We also saw evidence for: (1) a latency shift, particularly in the N1-P2 arm—later for lose; (2) truncation of P2 for lose; (3) sometimes a development of a clear N2 for lose; and (4) sometimes a later, more peaked, and larger amplitude P300 for lose than for win.

In another set of guessing experiments involving eight subjects by Steinhauer of our laboratory, subjects decided before each trial whether they would bet 50¢, 25¢, or nothing, for that trial. Again, only vertex data have been analyzed. P300 was found to be larger the greater the value of the bet, as shown in Fig. 2. Even more interestingly, in otherwise identical sessions with the same subjects, a random-number program selected the value of the subject's bet and the subject was informed of that value prior to each trial. The whole level of P300 amplitude was shifted. When the computer selected the value of the bet, all P300s were half the size of those obtained when the subject selected the value of the bet. In the computer-bet condition, order tended to be preserved—larger stakes yielded larger P300s than smaller stakes—but less consistently than in the subject-bet condition.

The concept that the feedback stimulus may provide different degrees of information needs further elaboration. We have not limited the term feedback to those cases where it can be shown that the feedback provides information that alters data obtained in subsequent trials. Partly, this is because it seems reasonable to infer that systematic feedback almost always affects future evoked potentials and behavior, and when the question is examined directly, one finds that indeed it does. For example, in a guessing situation without telling subjects about the relative probabilities of two events, but simply letting the stimuli indicate whether guesses are right or wrong, most subjects will match the event probabilities. In discrimination situations, the story is more subtle, but evidence exists that feedback results in improved discrimination (Jenness, 1972a).

Tueting et al. (1970) and Friedman et al. (1973) have shown that in situations in which subjects match event probabilities, P300 is larger the smaller the obtained outcome probability. Outcome probability is a term that takes into account both stimulus probabilities and the subjects' guessing probabilities. The relationship was clearest for confirming feedback, but seemed to hold for disconfirming feedback as well. More recently, Campbell and Picton (1976), using feedback stimuli in a time estimation task, reported that P300 amplitude was more systematically related to the meaningful information content of the feedback stimulus than to the information content defined classically in terms of surprisal value (probability) of the stimulus.

Subtle sequential effects, particularly in P300, have been noted and related to the inferred sequential expectancy of the subject. In some studies, data have been averaged as a function of type of sequence (Levit et al. 1973; Sutton et al. 1978; Tueting et al. 1970). In other studies, single trials have been considered as a function of type of sequence (Squires et al., this volume).

Levit (1972) compared normal subjects, schizophrenic patients, and depressive patients in a guessing situation in which clicks and light flashes had a 50:50 probability. Normal subjects and depressive patients developed what we called ipsimodal expectations. In other words, when they received a light on a given trial, they more often guessed that on the next trial they would also receive a light; having received a sound, they more often guessed that on the next trial they would receive a sound. Schizophrenic patients were about 50:50 in their expectation. When P300 was examined as a function of modality of the stimulus in the previous trial, normals and depressives had

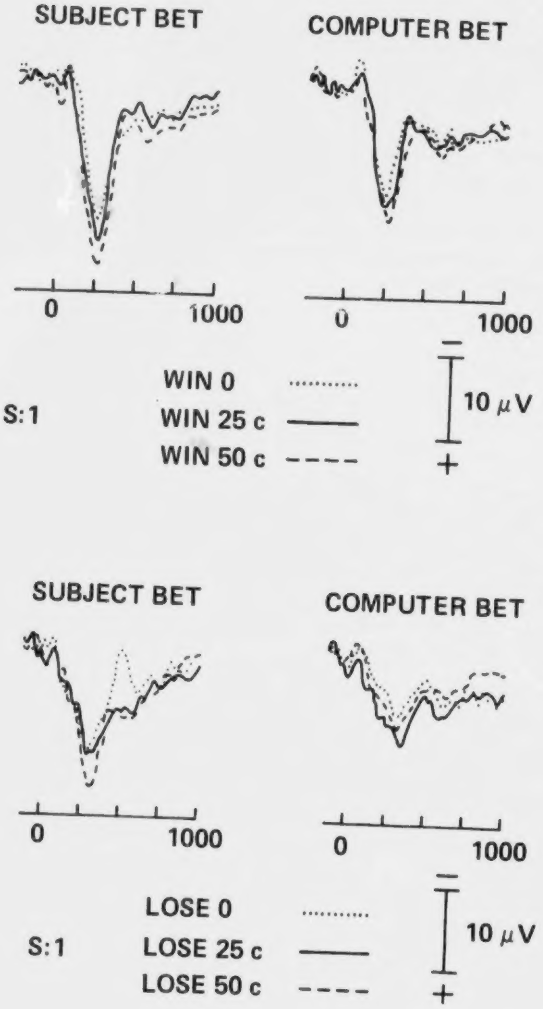

Fig. 2. Vertex auditory evoked potentials for one subject in a guessing paradigm. Negative at vertex is up with respect to a linked earlobe reference. Win and lose waveforms are compared as a function of the monetary value of the bet. Waveforms are also compared in a situation where the subject decided on the monetary value of the bet and in a situation where the computer decided on the monetary value of the bet.

larger P300s when the stimulus in the previous trial was in the other modality–just what one would expect on the basis of the notion that P300 is larger when the stimulus is relatively unexpected. For schizophrenics, no such difference was found. Admittedly, such evidence is indirect, but it is in the right direction, and it was inferred by examining both the behavioral and evoked potential data (see Sutton et al. 1978). Unfortunately, few studies have systematically related feedback to changes in both behavior and P300 (with the exception of Jeness 1972b and Leifer et al. 1976). More study of the effect of feedback on both behavior and P300 on future trials is greatly needed.

We would like to conclude by focussing on the concept of value or importance as an explanatory dimension in interpreting P300 findings. While we have no intention of suggesting that this variable provides an explanation of all P300 findings, the concept of the importance of the information provided by the stimulus appears to cross-cut a number of experimental designs that affect P300 amplitude. Perhaps target stimuli, in a sense by definition, are more important than nontarget stimuli. Perhaps, because of the way organisms are biologically constructed, rare events, novel events, or unexpected events may be inherently more important than nonorienting events. In the data presented here, winning 50¢ is more important to the subject than winning nothing. Placing a bet oneself is more involving, and in that sense more important, than observing the computer's luck, even if the subject collects the winnings or pays the losses. Perhaps the reason why P300 is sometimes larger for confirm and sometimes larger for disconfirm is that we have inadvertently made it more important for the subject to focus on either right or wrong outcomes in determining guessing strategy. An interacting variable may be variation among subjects. For personality reasons, some individuals may focus on winnings and others on losses. Experiments would need to be directed at these issues. Such an approach to the experimental analysis of P300 in the win-lose paradigm may be useful for other P300 paradigms as well.

Summary

The literature on whether P300 is larger when a feedback stimulus informs a subject that performance on a task is correct as opposed to incorrect was reviewed. We concluded that the relationship between P300 amplitude and direction of feedback continues to be inconsistent. Based on a re-analysis of the problem, a new experiment that yields more consistent findings was performed. Losing money yielded greater negativity in the P2-N2 region than winning money, no matter whether the rules were such that a correct guess resulted in losing or an incorrect guess resulted in losing. However, when the experimental design dissociated being correct or incorrect from winning or losing, in the sense that correctness or incorrectness could not influence the monetary outcome directly, being incorrect showed greater negativity in the P2-N2 region than being correct. With respect to P300, the effects were relatively weak; for more subjects P300 was larger for losing than for winning. But there was little difference in P300 for correctness and incorrectness when the experimental design isolated this variable from winning or losing.

In another experiment, P300 amplitude was larger the greater the size of the monetary bet placed on the guess. However, in a design in which the computer selected the monetary value of the bet to be placed, P300 amplitude was half the size obtained when the subject selected the monetary value of the bet to be placed. It should be noted that even when the computer selected the value of the bet, the subject pocketed the winnings or paid the losses.

It was suggested that the importance of information provided by the stimulus may be a key variable influencing P300 amplitude. A possible source of inconsistent findings with respect to P300 amplitude and right-wrong feedback might be that different experiments have inadvertently steered subjects into focussing on either being wrong or being right in guiding their strategy.

POTENTIALS ASSOCIATED WITH THE DETECTION OF INFREQUENT EVENTS IN A VISUAL DISPLAY

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As part of a project to investigate changes in vigilance over extended periods of time, electrophysiological events that accompany detection of infrequent events occurring in a continuously observed visual display were studied.

Method

The observer was seated 2 meters away from a 25-inch television monitor (16-deg angle subtended in the horizontal plane), on which a picture of a landscape was displayed from video tape (Cooper et al. 1977). At infrequent, irregular intervals (average 4 min) a vehicle—car, van, or lorry—crossed the display along any of four roads starting from left or right or from behind bushes in the centre. The observer was instructed to press a switch with his left thumb whenever he saw a vehicle and press another switch with his left index finger using a prearranged code to indicate the type of vehicle. The angle subtended by the vehicles was between 0.5 and 0.25 deg. The contrast of the picture was about 20%, and the brightness was set for comfortable viewing in the darkened room. A total of 24 events occurred during a 1.5-hr watch period.

In six subjects, recordings were taken from Fpz, Cz (compensated for eye movement), and Oz referred to commoned electrodes on the two mastoid processes and from bipolar montages 01-P3 and 02-P4. EEG and horizontal and vertical oculograms were recorded using amplifiers with an 8-sec time constant. In three additional subjects, electrodes were placed at Fpz, Fz, Cz, Pz, Oz, F3, F4, C3 C4, P3, P4, 01, 02, and 3 cm posterior to Oz. In these subjects, recordings of the oculograms were obtained. The upper frequency limit was 70Hz (-3dB). Respiration, EKG, galvanic skin response switch presses, and EMG of operant muscles were also recorded. Data channels were sampled at 100 points/sec and stored on digital tape of a PDP-12 computer. The sampling started shortly before the vehicle entered the display and ended 16 sec later.

Results

Detection time—i.e., the time between the entry of the vehicle onto the display and the switch press indicating detection—varied greatly across subjects, vehicles, and routes, with an average of 4.3 sec and a range of 0.4 to 25 sec. A further 2.4 ± 2 sec was required to recognize the vehicle.

Recordings of eye movements showed that up to 1 or 2 sec before detection (indicated by switch press) subjects were scanning the display as shown in a two-dimensional plot of eye position in Fig. 1. In this trial the vehicle was moving on a right to left track. At the start of this trial, the eyes were scanning near the vehicle, which had already entered the display, but the eyes then moved to the left at AB without seeing it. About 1 sec later (D) the eyes returned to the left and scanned the area of the display just below the vehicle. The eyes then moved upward, overshot the track at EF, and then locked onto the vehicle. The vertex EEG shows a large positivity at time EF, followed by the switch press indicating detection.

Multichannel recordings of the same event are shown in Fig. 2. Large positive potentials occur at the vertex and occipital midline electrodes. EMG begins to increase immediately after the positivity culminating in the button press 5.4 sec after the vehicle has entered the display.

All nine subjects developed this large positive potential between the time when an eye movement brought the gaze to the region of the vehicle and the switch press indicated detection. In 90% of the trials of all subjects, the potentials were identified in single trials stored on digital tape. The average amplitude at the vertex of this detection potential across nine subjects was 38 μV; mean amplitudes for individual subjects ranged from 20 to 63 μV. The field distribution is such that Cz and Pz are more or less equipotential and the field falls to about 60% at electrodes Fz, Oz P3, P4, C3 and C4 (Cooper et al. 1977).

The occurrence of this potential was not time-locked to the eye movement taking the eye into the target area, nor was it at a fixed time before the switch press that indicated detection. The frequency distribution of the times of occurrence of eye movements and switch press with respect to the positivity are

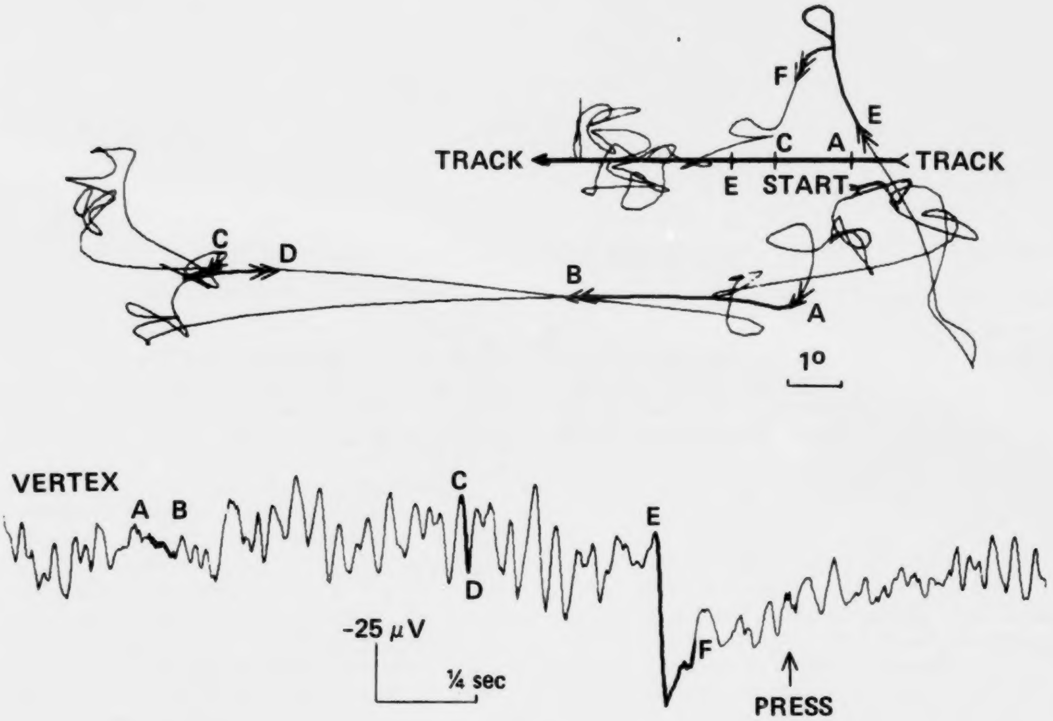

Fig. 1. Single-trial data showing eye position before and during acquisiton of a vehicle traveling from right to left. Vertex EEG is referred to commoned mastoid electrodes.

shown in Fig. 3. This shows that the most frequent times from positivity to switch press were between 200 and 300 msec. The distribution of the last large eye movement before the positivity was bimodal, and the most frequent times of occurrence were between 200 and 300 msec.

In seven subjects, detection positivity at the vertex occurred at the same time (±10 msec) as at the occipital; in two subjects the occipital preceded the vertex potential by 20 and 35 msec.

Slow potentials (SPs) were also recorded from scalp electrodes during the detection process, and most subjects showed increases of negativity at frontal, vertex, parietal, and occipital midline electrodes. SPs usually started at about the time of the last large eye movement before detection, but sometimes preceded this by 1 or 2 sec. In the trial shown in Fig. 2, SPs are most easily seen in the bipolar channels 02-P4 (ch 6). A clear CNV-like waveform was seen in averages time-locked to the last large eye movement before tracking (Fig. 4). These were prominent in the right and left bipolar channels, with the right being larger than the left (4 and 5). This SP lasted for about 3 sec and then reversed in polarity; a long-lasting negativity was seen at the vertex (ch 2). The bipolar channels were connected in such a way that a negative waveform occurring at the occipital electrode gave an upward deflection. Onset of this slow wave preceded the detection positivity and the start of tracking, but it was often difficult to determine the exact moment when the eyes locked on the vehicle.

Discussion

The degree of difficulty of the task, that is the detection of a small vehicle in a low contrast situation, probably accounts, more than inattention, for the fact that the vehicle was usually in the display for several seconds before being detected by the observer.

The first sign of events leading to a switch press indicating detection was an eye movement toward the target area. It is not clear from the present data whether this eye movement was part of the observer's natural scan pattern or whether it was triggered by the appearance of the vehicle in peripheral vision. Averages time-locked to eye movement (Fig. 4) show the start of a slow potential rise in the parietal-occipital region that suggests triggering, but there is no distinct evoked potential *before* movement that might

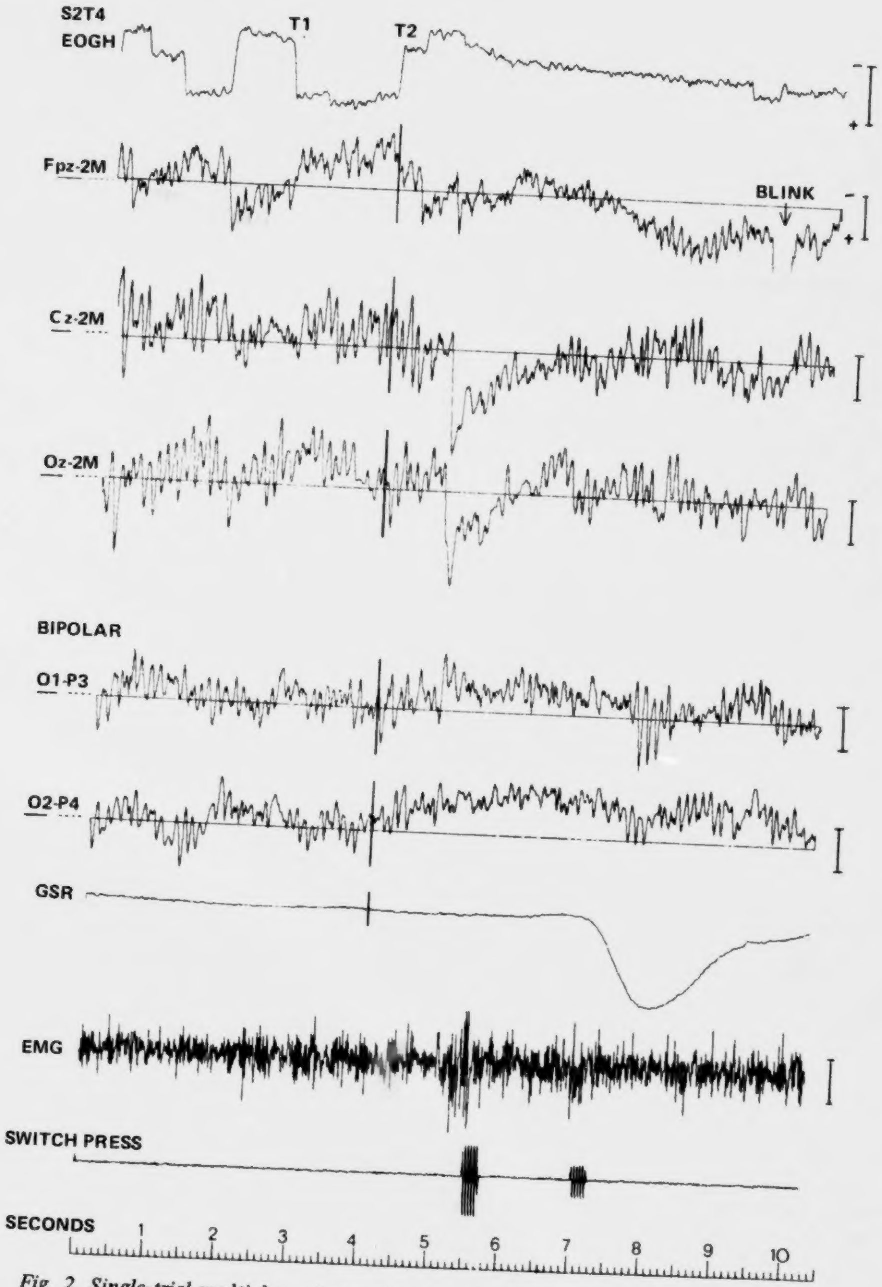

Fig. 2. Single-trial multichannel recording showing horizontal eye scan pattern (ch 1) with fixation and tracking (detection) occurring about 4 sec after the vehicle entered the display. Same trial as Fig. 1. A slow potential change started in the right posterior region (O2 - P4, ch 6) when the eye moved into the target area. A large positive potential occurred at about the time the eye fixated on the target and was largest at the vertex (ch 3), slightly smaller at the midline occipital (Oz)and hardly seen in the frontal region (Fpz). EMG (ch 8) and switch press (ch 9) occurred soon after the detection potential. T1 corresponds to AB in Fig. 1. Time T2 is the end of the saccade that takes the eye from the left of the display to the target area. Tracking starts shortly after this eye movement. Calibration of EOG, 250 μV; EEG and EMG, 25 μV. Negative up.

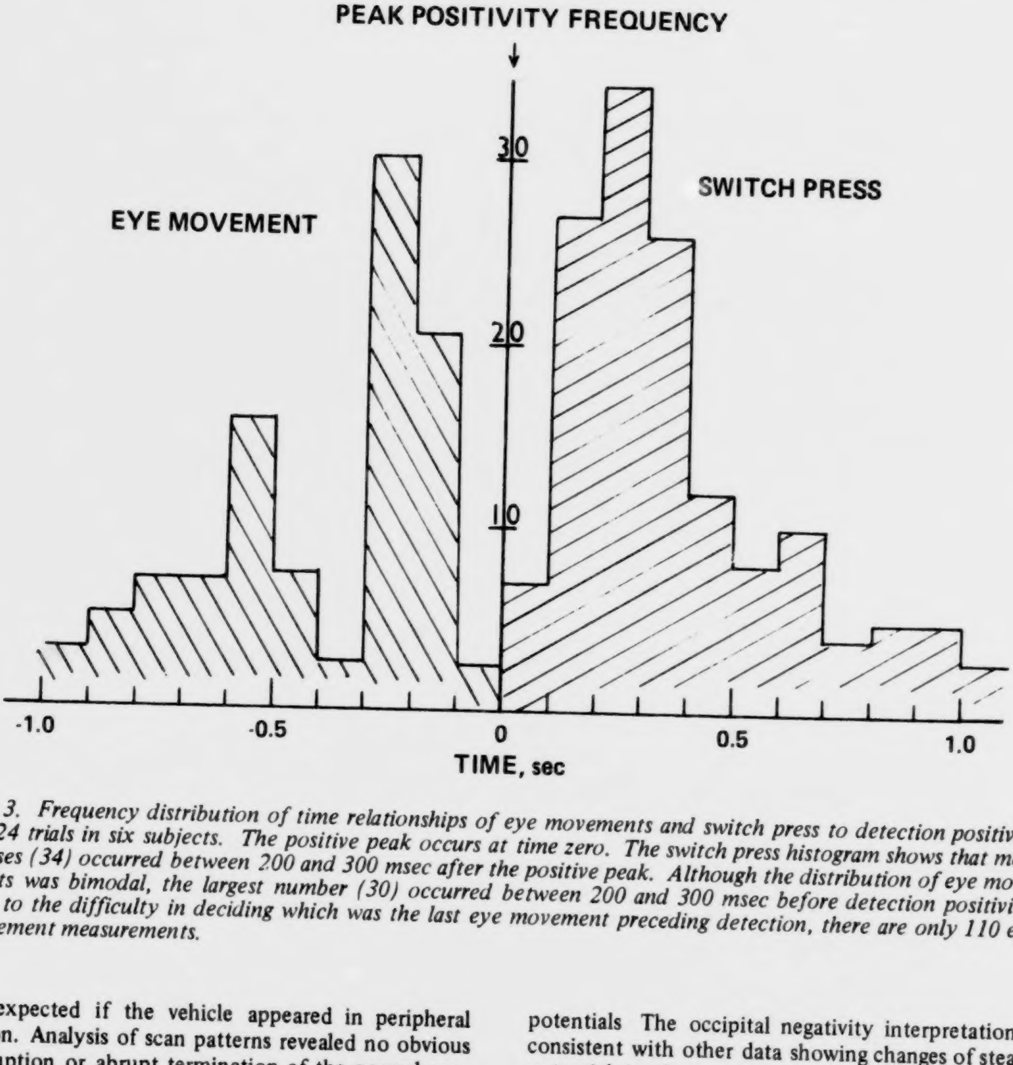

Fig. 3. Frequency distribution of time relationships of eye movements and switch press to detection positivity for 24 trials in six subjects. The positive peak occurs at time zero. The switch press histogram shows that most presses (34) occurred between 200 and 300 msec after the positive peak. Although the distribution of eye movements was bimodal, the largest number (30) occurred between 200 and 300 msec before detection positivity. Due to the difficulty in deciding which was the last eye movement preceding detection, there are only 110 eye movement measurements.

be expected if the vehicle appeared in peripheral vision. Analysis of scan patterns revealed no obvious disruption or abrupt termination of the normal scan immediately prior to detection, which might confirm triggering (interval T1 T2 in Fig. 2). However, since slow potential shifts started at this point in time, this eye movement toward the target area seems to have special significance.

The voltage distribution of slow potential shifts observed in these subjects was unusual in that it appeared in the occipital-parietal bipolar channel. There are two possible interpretations: (1) that a slow positive shift occurred at the parietal electrode or (2) that a negative shift occurred at the occipital electrode. Further information about the field distribution from occipital and vertex referential recordings is not easy to obtain since these recordings are confounded by the appearance of the larger positive detection potentials The occipital negativity interpretation is consistent with other data showing changes of steady potential in the occipital region during visual tasks (Kurtzberg and Vaughan 1977). This bipolar negativity lasted only a few seconds before changing polarity, a change that may be explained by an increasing negativity at the vertex (cf. ch 2 Fig. 4) spreading into the parietal area.

The large positive potential that occurred at about the time when tracking started has been called the detection positivity (Cooper et al. 1976). This potential showed very little reduction of amplitude during the 24 events and could usually be seen in the original data between the eye movement and switch press. It was maximum at the vertex and midline parietal area and spread into the occiput and frontal regions, but not to Fpz. It might be generated when the observer changed from a scanning to a tracking mode of eye

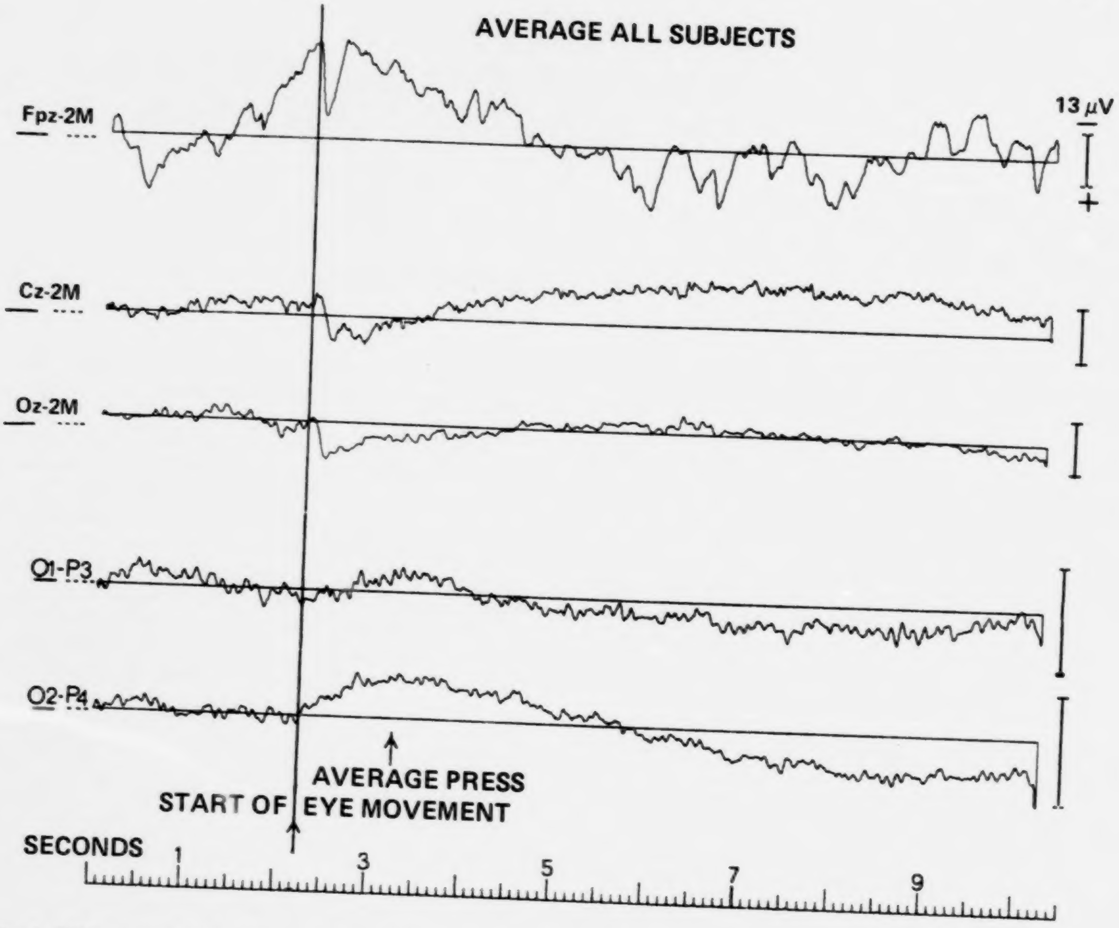

Fig. 4. EEG averages time-locked to the last large movement (time T2) before detection. EEG data were averaged across six subjects (about 20 trials each). The prefrontal channel shows a remnant of eye movement. The positivity at the vertex and occipital electrodes shortly after eye movement (vertical line) is the average of detection potentials imprecisely synchronized to eye movement. Note increasing negativity starting at eye movement in right bipolar recording and long-lasting negativity at vertex. Time constant, 8 sec.

movement, or it may represent the confirmation of a visual event being matched against a particular set or expectation. If the latter were the case, the potential would clearly have much in common with the P300, especially since the last eye movement often preceded the detection potential by 200 to 300 msec (Fig. 3). P300 latency is known to vary considerably according to circumstances. Similar factors might account for the difficulty in establishing a clear temporal relationship between detection positivity and environmental or other physiological events such as eye movements. Detection potentials occurred only to the detection of a vehicle and not to the identification of the type of vehicle, which occurred later. This observation is consistent with the concept of a match between the input signal and a neural template—in this case, of a vehicle.

Summary

The first electrophysiological sign of detection of an infrequent event occurring in a visual display is a slow rise of negativity at vertex, parietal, and occipital electrodes. This response usually starts about the time the gaze transfers to the area of the display containing the event. A large positive potential, which seems to appear when the presence of the target is confirmed, follows. The switch press indicating detection follows about 300 msec later.

ANALYSIS OF NONSIGNAL EVOKED CORTICAL POTENTIALS IN TWO KINDS OF VIGILANCE TASKS

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A number of investigators have reported that when the ratio of signals to nonsignals is 1:10, signals elicit P300s but nonsignals do not (Hillyard et al. 1973, Ritter and Vaughan 1969, Squires et al. 1975). Using language stimuli, Friedman et al. (1975) found that nonsignals did elicit P300s, possibly due to the engagement of the P300 system by verbal stimuli (cf. Galambos et al. 1975). The amplitude of P300 to nonsignals could be related to the degree of processing required by linguistic analysis, as well as to the relative frequency of nonsignals (Friedman et al. 1973, Tueting et al. 1970).

In order to shed light on the factors affecting nonsignal P300 amplitude, two experiments were devised; in one, the degree of information processing required by nonsignals was manipulated, and in the other, the relative frequency of signals to nonsignals was manipulated. Two kinds of vigilance tasks were used in the first experiment. In one condition, subjects were instructed to respond to a specific target, and in the other condition, to any stimulus that occurred twice in succession. The processing demands of the latter task were greater because each nonsignal had to be remembered for comparison with the next stimulus to see whether it was a signal. In the second experiment using only the single-target task, the relative frequency of nonsignals was manipulated in two ways ways–by varying the percentage of nonsignals and signals and by varying whether the nonsignals were comprised of many different stimuli or only one stimulus.

General procedures

Subjects ranged in age from 27 to 45; all had previous experience in evoked potential experiments.

Electrical activity was recorded from nonpolarizable Ag/AgCl electrodes at Fz, Cz, Pz, Oz, and above the right eye, referred to the right earlobe. The amplifier time-constant was 1 sec. For two subjects, EOG was recorded from left and right outer canthi to monitor possible lateral eye movements.

Visual stimuli, 50 msec in duration, were monitored from a DEC VR-14 slave scope by videocamera and presented at an interstimulus interval of 1.5 sec on a video monitor with a central fixation point. The monitor was continuously illuminated, and the stimuli were of moderate intensity and subtended a visual angle of 2 deg 20 min. Stimulus presentation and data acquisition were controlled by a PDP 11/10 computer. EEG was digitized every 4 msec to obtain a 100-msec prestimulus baseline and 1000-msec poststimulus epoch; data were stored on digital tape for off-line analysis.

Results

Experiment 1

Stimuli in each task were the numbers 02 to 19, presented in Task A in blocks of 60 and in Task B in blocks of 64. In Task A, the signal number 08 occurred 15 times per block, and 15 of the numbers from 02 to 19 occurred 3 times each per block for a total of 45 nonsignals. In Task B, signals were the repetition of any immediately preceding number. Signals occurred 16 times per block; and nonsignals, which were 12 of the numbers from 02 to 19, occurred 4 times each per block, for a total of 48 nonsignals. The ratio of signals to nonsignals was 1:4 in both tasks. Tasks were alternated for a total of eight blocks of each with the order of tasks counterbalanced across subjects. Subjects were instructed to respond to signals with a brisk wrist extension and rectified EMG was used to record reaction time. Averages for each subject were computed across blocks for 120 signals and 360 nonsignals (Task A) and for 128 signals and 384 nonsignals (Task B).

Averaged evoked potentials for two subjects to each stimulus class in the two tasks are presented in Fig. 1. The mean topographic distribution of P300

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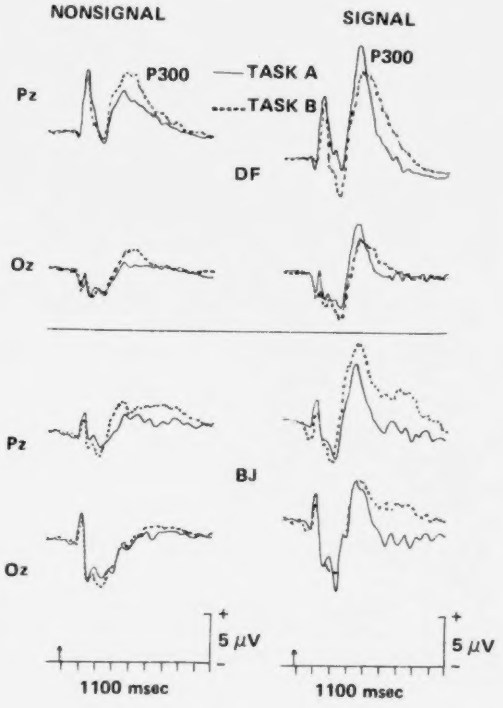

Fig. 1. Averaged evoked potentials from parietal and occipital electrodes for two subjects. A complete experimental protocol is shown. Stimulus onset at 100 msec. Time lines every 110 msec.

across the four subjects measured from the prestimulus baseline is presented in Fig 2. P300 to both the signals and nonsignals had a parietal focus. T-tests for correlated means were used to assess significance. Because multiple comparisons were performed, the Bonferroni criterion (Hays 1963) was used to correct for the number of tests. A corrected alpha level of 0.05 was used and only those t-values that had an associated probability of .01 or less were accepted as significant. P300 amplitudes to signals in both conditions did not differ significantly and were always larger than the respective nonsignal P300. P300 to nonsignals in Task B was of larger amplitude than P300 to nonsignals in Task A at Fz ($p < .001$), Cz ($p < .005$), and Pz ($p < .001$), but not at Oz ($p < .05$).

The findings indicate a large task-specific effect of processing complexity on P300 amplitude to nonsignals, an effect that is independent of probability. Reaction time analyses revealed longer reaction times to Task B signals (mean=480 msec) than to Task A signals (mean=451 msec), showing an effect of processing complexity on behavioral responses as well.

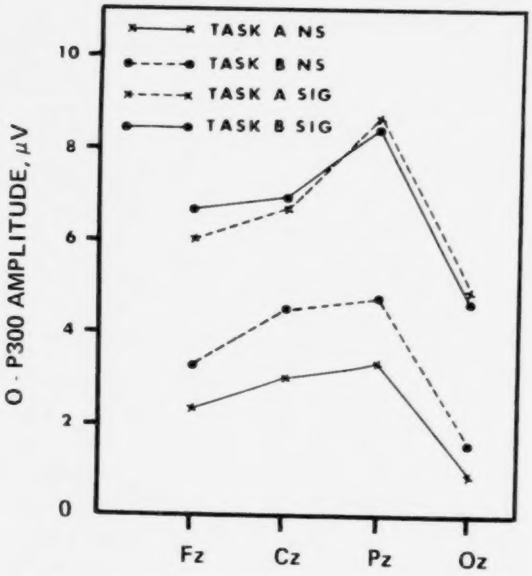

Fig 2. Mean baseline to peak P300 amplitude for four subjects. Data for signals (SIG) and nonsignals (NS) from each task are shown.

To check the intrasubject reliability of these findings, the data of subjects BJ and DF were divided into first-half and second-half averages. In both cases, the effect of task demands on nonsignal P300 amplitude was replicated in each half of the experiment. In fact, the experiment was repeated with subject BJ a week later, and the results were the same. EOG recording revealed no appreciable lateral or vertical eye movements. Vertical EOG was extremely low amplitude and did not show any systematic changes between or within conditions.

Experiment 2

In Task A of Experiment 1, clear P300 components were observed in nonsignal waveforms where the probability of the class of nonsignals was 0.75 and where each nonsignal occurred with a probability of 0.05. To test the hypothesis that P300 to nonsignals in this situation was affected by the probability of a given nonsignal, additional experiments were run in which blocks of trials with many different nonsignals (15, three times each, yielding a probability of 0.05 for each were alternated with blocks where only one nonsignal (the number 02 with a probability of 0.75) occurred. The signal (08), and other procedures were the same as Task A of Experiment 1. Two subjects served for eight blocks of each condition. As shown on the left side of Fig. 3, P300 to nonsignals was present and of equal amplitude in both conditions. Signal P300s were also equivalent in these two conditions.

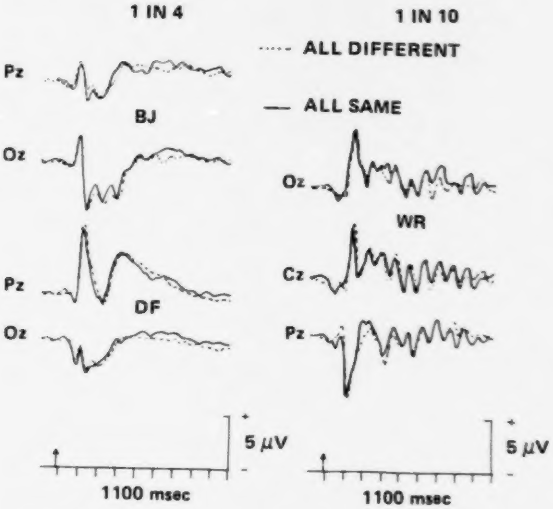

Fig 3. Left-hand panel: Nonsignal stimuli from a condition in which they occurred 75 percent of the time taken together and 5 percent for a given nonsignal (all different) or 75 percent for one nonsignal (all same); N is 360 per averaged response. Right-hand panel: Nonsignal stimuli where the probability taken together was 0.90 and approximately 0.06 for a given nonsignal (all different) and 0.90 for one nonsignal (all same); N is 108 per averaged response.

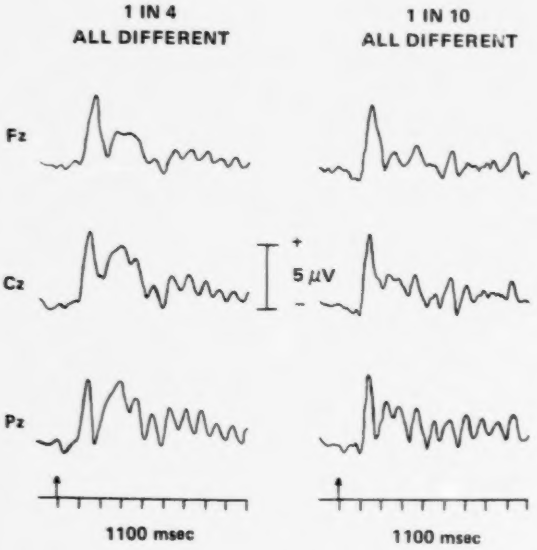

Fig. 4. Comparison of waveforms to nonsignal stimuli from one subject (WR) in conditions where taken together they occurred with a probability of 0.75 (1:4) or 0.90 (1:10).

Since the usual vigilance situation is one in which the ratio of signals to nonsignals is lower (e.g., 1 in 10), an additional experiment was conducted using the same procedure described above, but with a signal/nonsignal ratio of 1:10. Two alternating blocks with all different nonsignals (probability = 0.06 for each and a class probability of 0.90), or a single nonsignal (probability = 0.90) were run with one subject (WR). Waveforms on the right side in Fig. 3 disclose that for the 1:10 ratios, P300s are not discernible regardless of the probability of individual nonsignals. Furthermore, for this same subject (Fig. 4), comparison of nonsignal waveforms in the 1:4 conditions (class probability = 0.75) with nonsignal waveforms in the 1:10 condition (class probability = 0.90) shows that P300 is unobservable when the probability is increased to 0.90.

Although preliminary, these results suggest that P300 amplitude in a simple vigilance situation is an inverse function of the probability of occurrence of nonsignals taken as a class rather than the probability of a given nonsignal, and that at greater nonsignal densities P300 may not be observable in nonsignal waveforms at all.

Discussion

The results indicate that P300s are elicited by nonsignal stimuli, and their production is dependent upon two factors: (1) processing demands of nonsignals and (2) probability of a class of nonsignals and not probability of a given nonsignal within that class (see Friedman et al. 1975). These findings suggest the hypothesis that these two factors interact in producing P300 amplitude changes to nonsignal stimuli. When probabilities are equivalent (as in Tasks A and B) but processing demands differ, P300 amplitude will be larger to the nonsignal stimuli that require greater processing. When probability is high (e.g., 0.9) and task demands are not great (as in Task A), nonsignal stimuli will not elicit observable P300s at the scalp. The type of cognitive processing required in Task A was not sufficient to produce P300s at a nonsignal probability of 0.90, whereas subject WR had discernible P300s to the same nonsignal stimuli at a probability of 0.75.

Task B experiments in which the ratio of signals to nonsignals is 1:10 are now being carried out. If P300s are present to these nonsignal stimuli when processing demands are greater, this will confirm the hypothesis that both probability and processing demands interact to alter nonsignal P300 amplitude.

It is possible that differential attention favoring the nonsignals of Task B contributed to the observed effect. In one subject, longer analysis times revealed no consistent negative slow wave development between successive nonsignals in either task, ruling out CNV return as a factor in this result. In Task A, the standard vigilance situation, the subject simply has to determine the presence or absence of the signal on any given trial (long-term template match). In Task B, the subject must store each nonsignal in memory and wait for the next to see if it recurs (short-term template match). Longer reaction times to Task B signals are consistent with the suggestion of increased processing load in that condition.

The finding that class probability and not the probability of a given nonsignal affects P300 amplitude can be generalized to signals in these tasks. In experiment 1, signals of Tasks A and B occurred with a class probability of 0.25, but each different signal in Task B had a much lower probability of occurrence (approximately 0.015). However, signal-evoked P300 amplitude did not differ between tasks.

The finding that probability affects nonsignal P300 amplitude is consistent with the results of Squires et al. (1975) who found P300s to nonsignals when probability was 0.50. The fact that P300s were not seen to nonsignals when they occurred 90 percent of the time does not necessarily mean that there was no P300 brain response to these stimuli. Rather, the probability findings suggest that, when nonsignals occur 90 percent of the time, the brain's response is too small to be seen at scalp electrodes.

In summary, these experiments demonstrate that nonsignal P300 amplitude is positively related to the degree of cognitive processing required by nonsignal stimuli, as demonstrated for signal P300s in a wide variety of cognitive tasks (e.g., Donchin et al. 1973, Poon et al. 1976, Friedman et al. 1975), is negatively related to the frequency of the class comprising nonsignals, and is unrelated to the probability of any particular nonsignal within such a class. The data implicate memory storage and/or retrieval as a possible functional correlate of P300, and suggest that one should be able to manipulate P300 amplitude by changing the complexity of memory storage or search.

Summary

Visual evoked potentials were recorded from four subjects in response to numeric stimuli during two kinds of vigilance tasks in which the signal-to-nonsignal ratio was 1:4. In Task A, subjects were required to respond to the same stimulus (08) throughout a block of trials; and in Task B, subjects were required to respond to any stimulus that occurred twice in succession. Signal stimuli from the two tasks produced similar-amplitude P300s, while nonsignals of Task B produced significantly greater P300 amplitudes than nonsignals of Task A. This P300 amplitude difference reflected the greater processing demands of nonsignals in Task B, since in that task subjects were required to remember each nonsignal and then wait to see if the number recurred.

A second experiment assessed the effect of nonsignal probability on P300 amplitude by requiring the same response as in Task A with the same signal-to-nonsignal ratio (1:4), but with a change in the relative probability of each nonsignal. In one condition, the same nonsignal (02) was used throughout, and in a second condition several nonsignals (each with a relative probability of 0.05) were used. No difference in nonsignal P300 amplitude was found, which indicates that the probability of a class of nonsignals rather than the probability of individual nonsignals affected P300 amplitude. In part 2 of this experiment, a signal-to-nonsignal ratio of 1:10 was used, with either the same or different nonsignals. No P300s to nonsignals in either condition were observed. Collectively, these findings (1) demonstrate that P300 amplitude to nonsignal stimuli is dependent upon both the probability of a class of nonsignal stimuli and on the processing demands elicited by these nonsignal stimuli, and (2) suggest that these two factors interact in affecting nonsignal P300 amplitude.

Acknowledgments

The authors wish to thank Dr. L. Erlenmeyer-Kimling, in whose laboratory this research was performed, and Mr. Jim Hollenberg for computer programs used in this study.

VARIATIONS IN THE LATENCY OF P300 AS A FUNCTION OF VARIATIONS IN SEMANTIC CATEGORIZATIONS[1]

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Several recent studies of P300 (Ritter and Vaughan 1969, Tueting et al. 1970, Squires et al. 1977) utilized the following experimental paradigm: the subject is presented with a stream of stimuli, each of which may belong to one of two categories. The subject counts and reports the number of stimuli that belong to one of the two categories. The probability is low that a stimulus will belong to one of the categories and correspondingly high that it will belong to the other category. Stimuli in the low-probability category were found to elicit an enhanced P300 component. In most experiments reported to date, categorizations were based on physical features of stimuli, such as the frequency of tones, hue of light flashes, or specific pattern of the visual stimulus. It seemed necessary to determine if the same results would be observed if the categorization required of the subject was based on semantic features of the stimuli (cf. Friedman et al. 1975).

For this purpose, subjects were presented with sequences of words, each of which could be categorized, on the basis of a semantic rule, into one of two categories. The two categories appeared with the probability of either 0.20 or 0.80. The intent was to determine the extent to which the appearance of stimuli belonging to the rare category would enhance the P300 component. As the complexity and latency of the categorization response varied with semantic categories, the relationship between the duration of cognitive operations and the latency of the P300 component could also be examined. If P300 reflects specific cognitive processing activity (Donchin 1975, Donchin et al. 1973), then the latency of P300 relative to the physical stimulus would depend upon the latency and duration of the cognitive process and would vary as a function of its complexity. This proposition was tested in the present study.

Methods

The experiment utilized PLATO, a computer-assisted instruction system developed at the University of Illinois. The PLATO terminal uses a plasma panel for display (Smith and Sherwood 1976). The display is achieved by illuminating any of 512 x 512 luminous dots. In this experiment, the PLATO system was programmed to present a sequence of words on the terminal, one at a time every 2000 msec. Each word was preceded by an external trigger, which was led to a PDP-8/E computer. The trigger activated the digitizing process so that EEG data would be acquired in relation to the presentation of the stimuli.

Data from three studies are reported. In each study, subjects were presented with four different sequences of words. Each sequence consisted of about 200 words selected randomly on each trial with the appropriate probability. The following series were used:

1. *Fixed names.* The words were either "Nancy" or "David." "Nancy" appeared 20% of the time.
2. *Variable names.* Words were selected from a list of 20 female or 20 male names. Each name was a two-syllable word consisting of five letters. Twenty percent of the names were selected from the female name list and 80% from the male name list.
3. *Rhymes.* Words were selected either from a list of different words rhyming with "cake" or from a list of 20 four- or five-letter nonrhyming one-syllable words. Rhymes were presented 20% of the time.[3]
4. *Synonyms.* Words were selected from a list of 20 arbitrarily chosen words and 9 synonyms of the word "prod." Synonyms were presented 20% of the time.[4]

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[1] An extended report of these experiments has been published elsewhere (Kutas et al. 1977).

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[3] The nine words rhyming were: bake, rake, stake, lake, make, fake, wake, flake, and take. In the second experiment, the words ache and steak were included.

[4] The synonyms presented were goad, poke, shove, nudge, urge, push, prompt, spur, and press.

Brain potentials were monitored with Burden electrodes placed at Fz, Cz, Pz, C3, and C4 referred to linked mastoids in the first experiment and to the chin in others. EOG was recorded between supraorbital and canthal positions. The subject was grounded on the forehead. EEG was recorded on analog tape with a 2-sec time constant and 30-Hz high-frequency cutoff amplitude. Data were digitized off-line by an IBM 1800 computer and stored on digital magnetic tape. Digitizing started 220 msec prior to the stimulus and ended 780 msec after the stimulus. The sampling rate was 10 msec per point. A PDP-8/E computer determined, on line, whether eye movement artifacts were present during each trial by comparing EOG variance to a criterion value.[5] Contaminated trials were not included in the average (the synchronizing pulse on the analog tape was inhibited).

Subjects sat in a comfortable chair in a semi-darkened, shielded room and completed the four conditions in the following order: fixed names, variable names, rhymes, and synonyms. Prior to each block of trials, the subject was instructed to watch the words and count stimuli from the rare category. At the end of each run, the subject was asked to report his count. Each condition consisted of approximately 200 trials (40 rares).

Results and discussion

Experiment 1

Six subjects participated in the first experiment. in which the task was to count the number of stimuli belonging to the rare category. Fig. 1 presents the data from one subject and superaverages computed over the entire subject group.

Evoked responses elicited by stimuli belonging to the frequent category lack a P300 component, while ERPs elicited by stimuli belonging to the rare category show a marked P300 component. Latency of the P300 component varied widely–shortest for the fixed name categorization and the longest for synonyms. Variable names and rhyming words showed intermediate latencies. The same order of latencies characterized data from all subjects. P300 amplitude elicited during the fixed-name condition was larger than in the other three conditions. There were no systematic differences among the amplitudes of the average P300s.

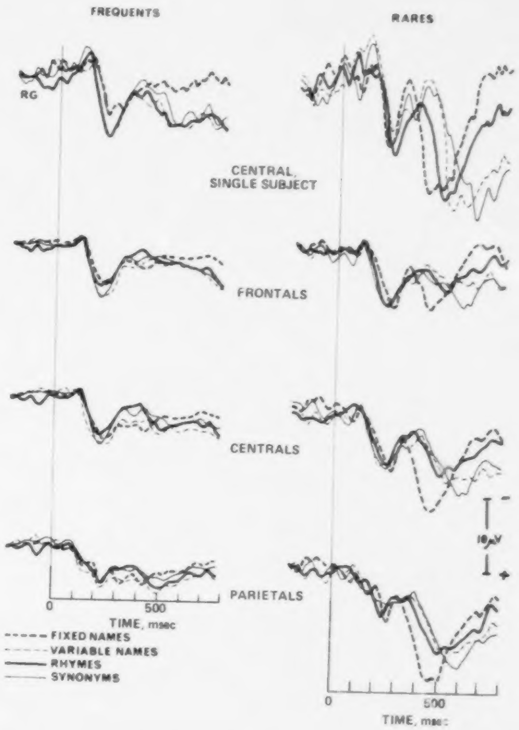

Fig. 1. Superimpositions of average ERPs obtained during experimental conditions requiring different semantic categorizations. At the top are sample Cz waveforms to the rare and requent stimuli from an individual subject. The remaining waveforms are superaverages across six subjects for Fz, Cz, and Pz positions. Only the rare stimuli (prob. = 0.20) were counted. Each rare waveform consists of approximately 18 to 30 single trials.

These data demonstrated that the P300 response was associated with the categorization of stimuli even when categorization depended upon semantic rather than physical characteristics of stimuli. Although averaging was over a diverse array of physical stimuli, such as different female names, a clear P300 response was elicited. The data were consistent with the suggestion that P300 latency varies systematically with the complexity of information processing required.

Experiment 2

To validate the extent to which differences between series were related to different subject decision times, the experiment was repeated with five other subjects, who were asked to respond rapidly by pressing one of two buttons upon the appearance of any stimulus from the two categories. The results, shown in Fig. 2, differ from those obtained in Experiment 1 in two important respects. First, it appeared that the execution of a motor response changed the appearance of the "frequent" evoked response in that

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[5] Trials were rejected if the sum of squared digitized values (220 msec prestimulus and 780 msec poststimulus) exceeded a criterion value determined by visual inspection of a large sample of EOG traces and their corresponding digital values.

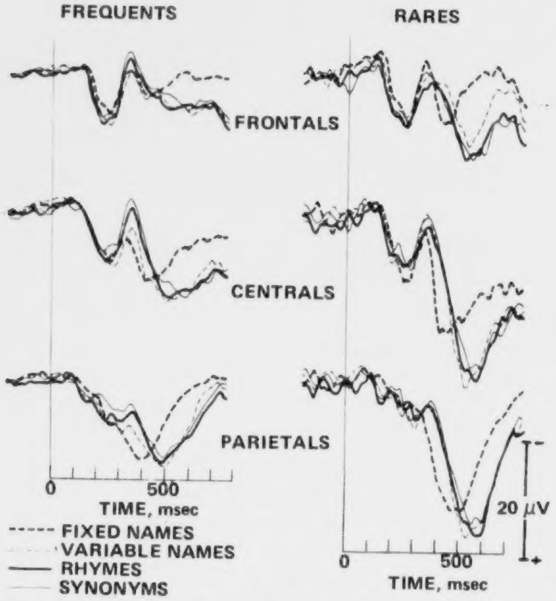

Fig. 2. Superimpositions of ERPs averaged across five subjects from four different experimental conditions. Subjects were required to perform a choice reaction time response, responding to frequent stimuli with one hand and rare stimuli with the other.

a positive component, presumably P2 of the motor potential, could be observed. This positivity could not fully account for the marked enhancement of positivity with a latency of about 400 msec associated with rare stimuli. Latencies obtained in this second experiment, however, were somewhat less differentiated than those observed in the first experiment. The fixed-name latency was still considerably shorter than that associated with the other three conditions; however, these three conditions were no longer as differentiated as they were during the count condition. Table 1 presents means and standard deviations of reaction times (RT) averaged over the five subjects for each of the experimental conditions. These means are based on RT scores obtained from all trials on which subjects responded correctly. The large variance of RT is noteworthy. The fixed-name RT was substantially shorter than the RT of the other conditions, which were essentially equal. The variance of P300 latency (Fig. 2) was equally large, suggesting a substantial degree of trial-by-trial variation in P300 latency and RT. An analysis of the relationship between P300 latency and RT is presented by Kutas et al. (1977).

Failure to observe differences in P300 latency with three of four experimental conditions could be attributed to the fact that in the second experiment speed of response was emphasized without requiring accuracy in categorization. Thus, subjects tended to execute erroneous categorizations as they attempted to maximize response speed. The error rate varied across experimental conditions, with fewest errors occurring during the fixed-name condition and most occurring during the synonym condition. Clearly, subjects could have traded accuracy for speed. A third experiment was therefore run to assess this possibility.

Experiment 3

In the final experiment, the rhyme series was not used. Five subjects participated under three experimental conditions with each of the remaining series. The "count" condition replicated Experiment 1 and the "RT-accuracy" condition subjects made a choice reaction to the stimulus, but were instructed to be very accurate. The results are shown in Fig. 3. When accuracy was emphasized, P300 latencies varied in the same manner as in the count condition. When speed was a prime consideration, subjects seemed to maximize speed by reducing processing time invested

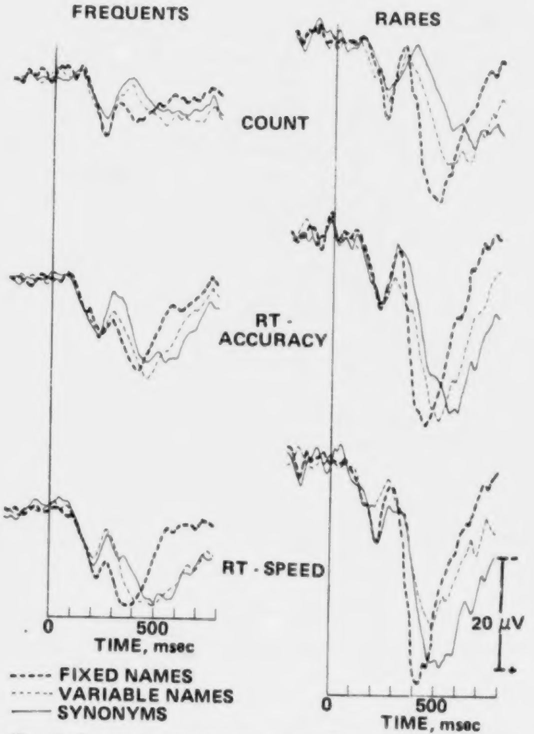

Fig. 3. Superimposition of central (Cz) ERPs averaged across five subjects for three semantic categorizations obtained during three different response regimes.

Table 1. Means and Standard Deviations of Reaction Times, Experiment 2 (RT-speed, five subjects)

Condition	Rare stimuli		Frequent stimuli	
	Mean RT	Standard deviation	Mean RT	Standard deviation
Fixed names	514.41	83.31	419.43	96.88
Variable names	613.25	89.82	522.22	107.24
Rhymes	633.48	123.79	524.22	125.39
Synonyms	666.55	109.43	513.48	105.78

Table 2. Grand Means and Standard Deviations of Reaction Times, Experiment 3 (Count, RT-accuracy, RT-speed, five subjects)

Condition	Rare stimuli		Frequent stimuli	
	Mean RT	Standard deviation	Mean RT	Standard deviation
Fixed names-accuracy	543.56	111.19	453.27	110.09
Variable names-accuracy	573.03	164.67	498.79	99.38
Synonyms-accuracy	619.73	100.60	520.25	119.56
Fixed names-speed	455.47	77.23	353.15	102.89
Variable names-speed	506.92	100.65	409.29	92.33
Synonyms-speed	531.43	94.70	413.75	96.99

in the categorization, thereby reducing the variability in P300 latency. Grand means and standard deviations of RT for the six conditions are presented in Table 2.

Conclusion

The latency of the late positive component (P300) associated with rare occurrences of relevant stimuli varies with stimulus evaluation time. The differences in P300 latency cannot be attributed to the effects of the motor response on P2. Latency differences observed during the count condition were quite similar to those observed in the RT-accuracy condition, yet no manual responses were required during count conditions. The data are consistent with the view that the variable-latency parietal-maximum, late positive waves are manifestations of the activity of the same intracranial processor. Alternate views that tend to differentiate between late positive components by their latency (e.g., Thatcher 1977) seem less parsimonious.

TOPOGRAPHICAL STUDY OF THE EMITTED POTENTIAL OBTAINED AFTER THE OMISSION OF AN EXPECTED VISUAL STIMULUS

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Several laboratories have reported a cerebral potential, the 'emitted potential,' following an expected but missing stimulus (Barlow et al. 1965; Sutton et al. 1967; Klinke et al. 1968; Ritter and Vaughan 1969; Barlow 1969; Weinberg et al. 1970, 1974; Picton and Hillyard 1974). The emitted potential is considered to be similar to th[illegible]tive component (P300) that peaks about 2[illegible]00 msec after a stimulus that provides information to the subject, especially under conditions of uncertainty (see review by Tueting, this section). Simson et al. (1976) and Renault and Lesevre (1976) have shown that the emitted positive potential is preceded by a negative component that usually peaks in the posterior region when the missing stimulus is visual. Moreover, Simson et al. (1976) demonstrated that this negative emitted component changed topography according to stimulus modality, whereas the positive wave did not.

Renault and Lesevre (1976) also showed that both the negative and the positive components of the emitted potential were made up of successive or overlapping peaks with various topographies. Latency variability in single trials due to the absence of a precisely timed external stimulus (Ruchkin and Sutton 1978) could explain these average successive peaks if they all had the same topography. Since this is not the case, emitted components were topographically analysed trial by trial in the present study, utilizing the spatiotemporal mapping method of Remond (1961). To test the possible topographical specificity of this phenomenon, a comparison was made between the missing visual stimulus potential and the early part of the visual evoked potential obtained with pattern stimulation.

Two experiments were conducted to evaluate successive or overlapping components of the emitted potential as related to different brain generators and psychophysiological mechanisms. In particular, the variation of these components with different tasks involving or not involving motor response was investigated. Topographical specificity of emitted potential components was then examined by comparing such potentials obtained under half-field stimulation conditions with potentials obtained under whole-field conditions and with the early part of the pattern evoked potential.

Methods

Five normal adults served as subjects. In the first experiment, three runs of 450 visual stimuli, each of the same type (whole-field stimulation), were recorded for each subject. The stimulus was a checkerboard projected at 1-sec intervals for a period of 20 msec on a screen, which had a fixation point in the center. During each run, 10% of the stimuli were randomly omitted. The response required of the subjects was different in each run:

1. Go condition–The subject was instructed to respond as quickly as possible *to the missing stimulus* with a right-finger displacement toward the right.
2. No-go condition–The subject was instructed to respond to each stimulus, but to *withhold response to the missing stimulus.*
3. Counting condition–The subject was instructed to *count the missing stimuli* mentally without motor response to the presentation or omission of the stimulus.

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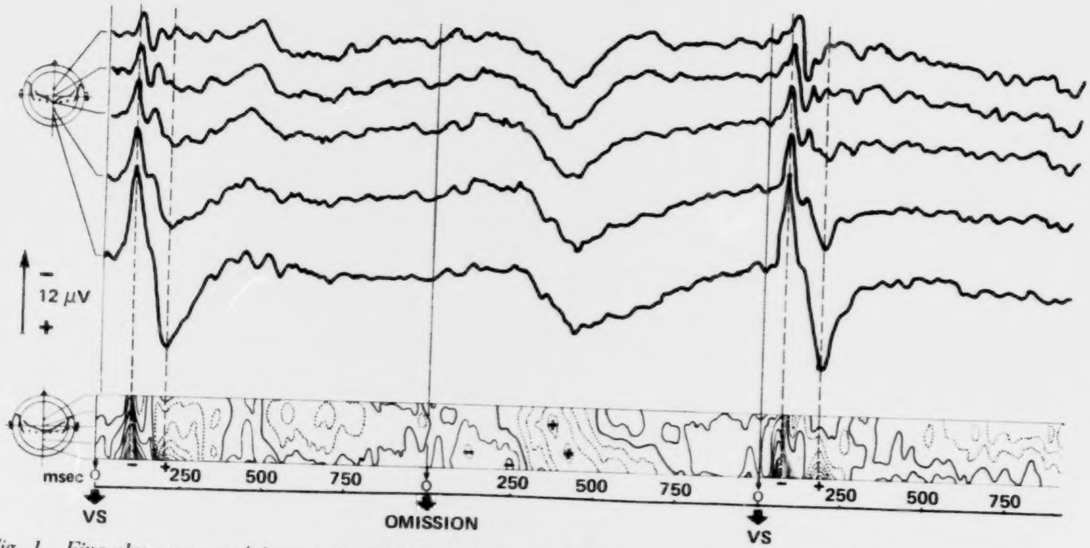

Fig. 1. *Five chronograms (above) obtained from the longitudinal part of the montage and the corresponding spatiotemporal map (below), representing the average emitted response to 45 missing stimuli occurring in a series of whole-field checkerboard stimulations during a counting task. The emitted potential is preceded and followed by average visual evoked potentials. On the time scale, 0 indicates the moment the stimulus should have appeared (omissions) or the occurrence of a visual stimulus (vs). On the map, the ordinate represents space, i.e., the location on the scalp of the five electrodes of the longitudinal arm of the montage. The values between two successive electrodes are obtained by mathematical interpolation. Amplitude is represented in the form of isopotential lines; in this figure, the potential increases in 2-µV steps from one isopotential line to the next. Thick lines indicate potential 0; thin lines indicate negative potentials; broken lines indicate positive potentials. Peaks are indicated by + or −. Pattern evoked potentials include N100 and P200 components peaking in the preoccipital region. The emitted potential is characterized by a negative wave that peaks (4 µV) at 125 msec in the parietal region and later in the preoccipital region, and a positive wave (8 µV) that peaks at the vertex (380 msec) and later in the parieto-occipital area (400 to 700 msec). Data from the same subject are shown in all figures.*

The second experiment also involved three runs of 450 visual stimuli. A different type of stimulation was employed in each run: (1) whole-field, (2) right half field, (3) left half-field. Subjects counted omissions, which occurred with 10% random probability.

Recordings were made with a montage of nine equally spaced electrodes 4 cm apart forming a cross. The longitudinal part of the cross was on the midline extending from 4 cm anterior to 12 cm posterior to the vertex (Cz). The transverse branch crossed midline 4 cm posterior to the vertex (approximately on the central sulcus) and extended 8 cm on the right and left. Each electrode was referred to linked ears. The time constant was 0.7 sec, with an upper bandpass limit of 220 Hz. Horizontal and vertical electrooculograms were recorded, and every response occurring during or after an eye movement was eliminated from the analysis.

On-line analog-to-digital conversion was done by computer at a 2-msec sampling rate and displayed in the form of chronograms and spatiotemporal maps (Remond 1961). Spatiotemporal maps were constructed from averaged data (45 responses to omissions for each run), as well as from single-trial data when possible. (Spatial interpolation acheived in the mapping process is itself a way of improving signal-to-noise ratio.)

Results

Average emitted potentials to missing stimuli

An average potential time-locked to the moment the visual stimulus should have appeared was observed in all subjects in go and no-go reaction time (RT) situations as well as the counting task. This potential consisted of a negative wave (N) followed by a positive wave (P) (Fig. 1 and 2 and Tables 1 and 2). Each of these averaged components usually consisted of at least two different components peaking at different times and locations on the longitudinal part of the montage. These components were designated Na, Nb, Pa, and Pb.

Whole-field stimulation: Table 1 shows mean latencies and amplitudes of emitted components

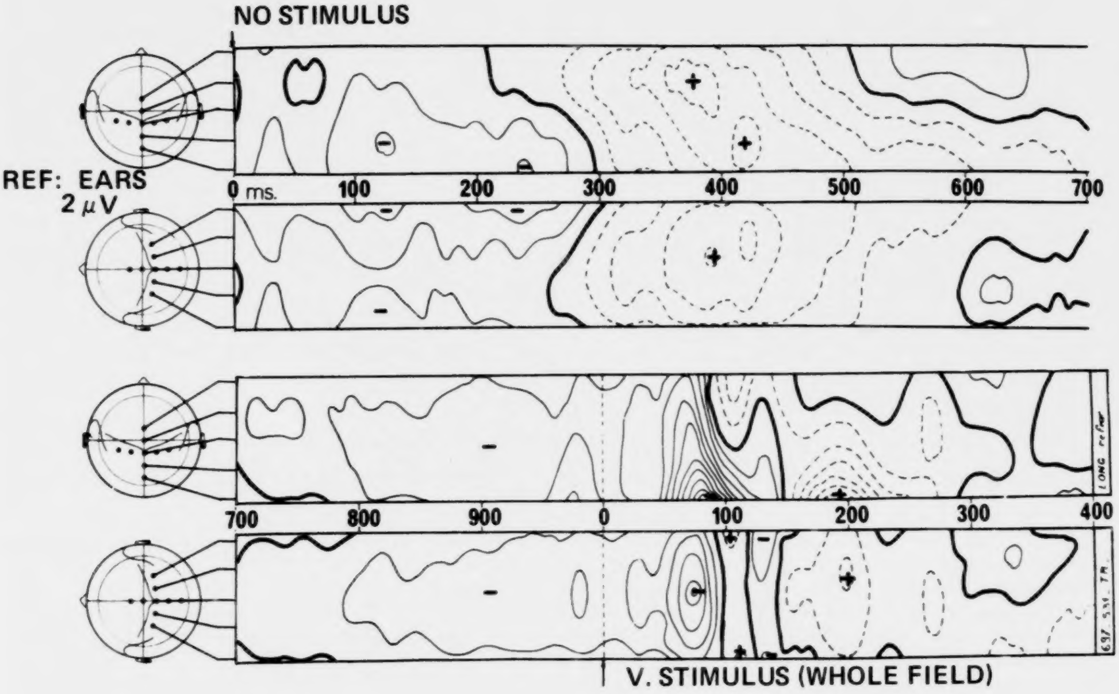

Fig 2. The upper map is an enlargement of the part of Fig. 1 corresponding to the emitted potential. Note the apparent flowing of the positive component from the frontocentral region toward the ocipital region. The second map represents the same event obtained on the transverse arm of the montage. The two bottom maps show the average pattern evoked potentials to the stimuli following omissions as obtained on the longitudinal and the transverse part of the montage. Isopotential steps are 2 μV.

(measured on the longtitudinal part of the montage) for the counting, go, and no-go conditions. Latencies and amplitudes varied widely among subjects in each experimental situation. Only the negative wave amplitude differed consistently according to the type of task; the negative component was larger in the go and no-go conditions than in the counting condition.

Table 2 indicates the topography of peaks on the longitudinal and transverse parts of the montage. The exact position of the longitudinal peaks (referred to Cz) varied among subjects, but the general spatial organization of each component was very similar for the five subjects. In the counting condition, topography of the first negative wave for four subjects was more posterior than that of the first positive wave. Spatiotemporal organization of the positive wave was quite similar in all subjects in that it always began to peak next to the vertex (Pa located at Cz ± 4 cm) and culminated later in the parietal or parieto-occipital region (Pb located 6 to 12 cm posterior to Cz). This longitudinal organization was seen under all three task conditions. For all subjects (12 situations out of 13) and all tasks, the negative component of the averaged transverse emitted potential was larger on the right hemisphere (3.7 μV) than left hemisphere (1.7 μV).

Reaction time was longer for all subjects when a motor response was required to omissions ($\bar{x}$=555 msec, S.D.=141 msec) than to non-omitted visual stimuli (x=314 msec, S.D.=100 msec).

Half-field stimulation: in the case of omissions occurring after half-field stimulation, three subjects (RR, BR, and NL) showed an asymmetrical negative peak (Na) located contralaterally in both situations (right-field and left-field). This contralaterality was never observed for the positive component. In the longitudinal plane, the NA component was always located in posterior regions. One of the remaining two subjects showed an ipsilateral peak during right-field stimulation, while the other had a midline peak in the same situation; thus, no comparison could be made.

Table 1. Mean Latency and Amplitude of Negative (N) and Positive (P) Components of the Emitted Potential Measured on the Longitudinal Montage during Whole-field Stimulation

	Counting				No/go				Go			
	Na	Nb	Pa	Pb	Na	Nb	Pa	Pb	Na	Nb	Pa	Pb
Latency, msec	178	321	469	565	150	280	451	594	132	272	371	535
(S.D.)	(33)	(94)	(97)	(97)	(32)	(62)	(83)	(100)	(34)	(30)	(44)	(64)
Amplitude, μV	2.8	2.6	4.4	4.7	3.9	5	4.6	3.9	3.07	4.7	5.1	4.8
(S.D.)	(0.7)	(1.2)	(1.5)	(2.7)	(2)	(1)	(3)	(1.2)	(0.6)	(3)	(4.2)	(2.4)

Table 2. Topography of Emitted Potentials during Whole-field Stimulation[a]

		Counting				No/go				Go			
Subject	Montage	Na	Nb	Pa	Pb	Na	Nb	Pa	Pb	Na	Nb	Pa	Pb
RR	Long.	+12	Cz	-2	+6	Cz		+4	+10	+4	+4	Cz	+8
	Tr.	8R	8R	MI	MI	4R		MI	MI	2R	MI	MI	Me
JF	Long.	+8	+12	Cz	+8	+6	+8	Cz	+4	+10	+8	-2	+6
	Tr.	8R,L	8R,L	MI	4R	8R	8R	MI	MI	8R	8R	4R	4R
JPJ	Long.	+4	Cz	+8	+10	+4	Cz	Cz	+8				
	Tr.	8R	8R,L	MI	MI	MI	MI	4L	4L				
BR	Long.	+10	+12	+4	+8			-4	+8	+4			
	Tr.	8R	8R	MI	MI			MI	MI	MI			
NL	Long.	+12	+12	Cz	+8		+12	Cz	+8		+12	+4	+10
	Tr.	4R	4R	MI	MI		4R	4L	MI		8R	MI	MI

[a] Location of peaks on the longitudinal and transverse part of the montage for three tasks. The location of longitudinal peaks is expressed in cm with respect to Cz, minus is anterior and plus is posterior to Cz. The location of transverse peaks is noted with respect to midline (MI), on the right (R), on the left (L), or bilateral (R,L).

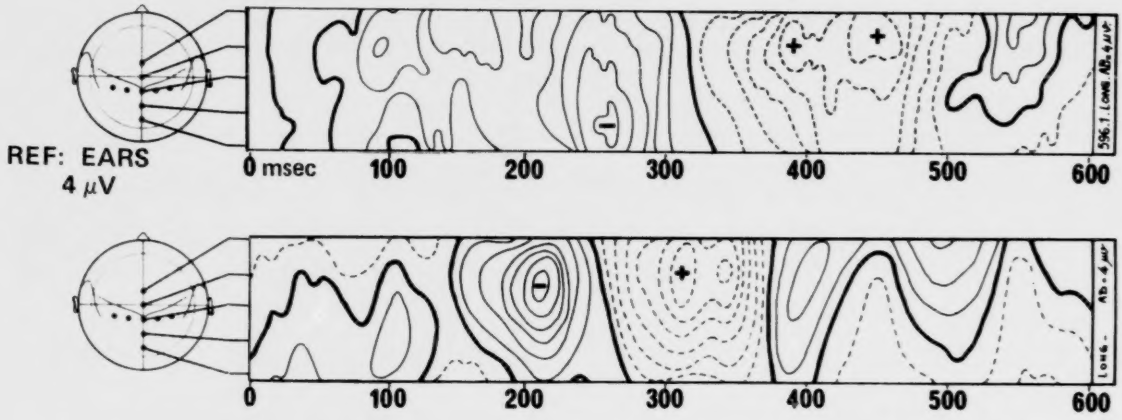

Fig. 3. Vertex patterns of single-trial emitted potentials following the omission of an expected visual stimulus in the no-go task run. Longitudinal part of the montage. Upper map: the negative wave peaks on the parieto-occipital region; the positive one at the vertex. Lower map: the negative and positive waves both peak at the vertex. Isopotential steps are 4 µV.

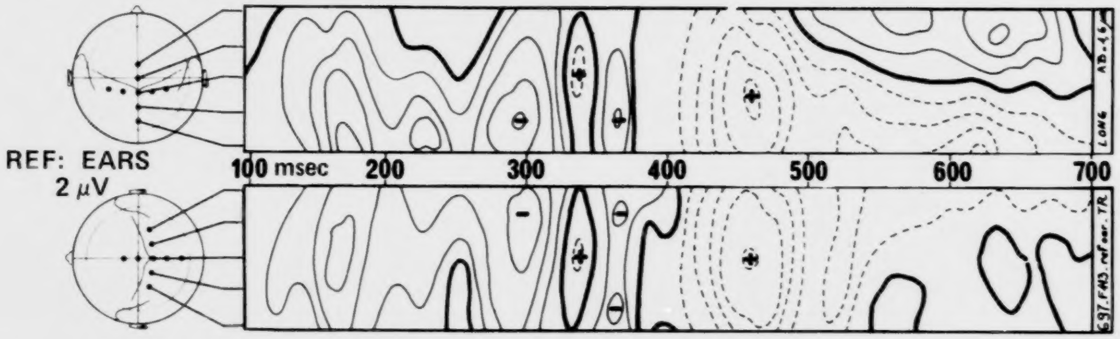

Fig. 4. Parietal pattern of single-trial emitted potential following the omission of an expected visual stimulus (cross montage). The first 100 msec following the omission are not represented. The long positive wave peaks first at 450 msec in the parietal region; and a second peak occurs 650 msec after the omission in the preoccipital region. It is preceded by at least three successive waves of short duration, also located in the parietal area. Note, especially in the transverse part of the montage, the similarity of this emitted pattern and the evoked potential of Fig. 2. Isopotential steps are 2 µV.

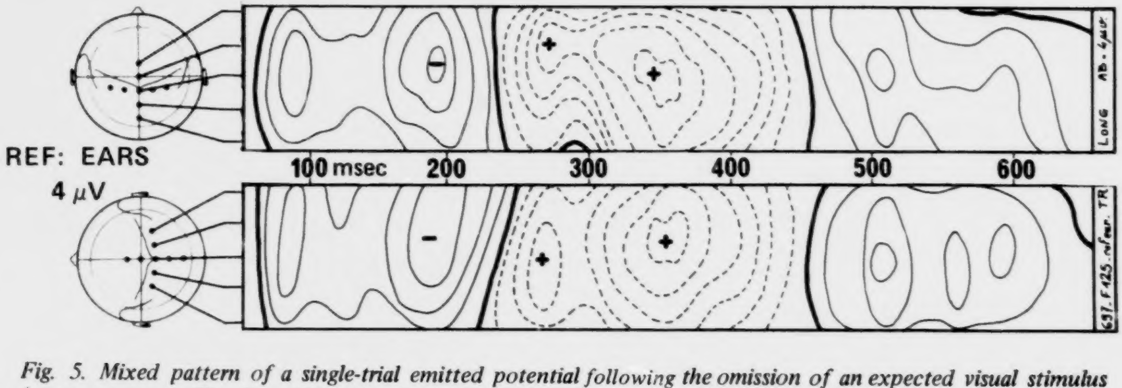

Fig. 5. Mixed pattern of a single-trial emitted potential following the omission of an expected visual stimulus (cross montage). The first 100 msec following the omission are not represented. This emitted potential looks like the spatiotemporal addition of the maps of Fig. 3 and 4. Isopotential steps are 4 µV.

Single-trial analysis of emitted potentials

Single-trial spatiotemporal maps were constructed for the five subjects (45 trials x 3 tasks=135 maps per subject). With the exception of subject JF who emitted very high-amplitude potentials, only approximately 60% of single-trial waveforms could be detected due to the low signal-to-noise ratio.

Figs. 3-5 depict different topographical patterns of emitted potentials observed in these single-trial maps. Positive components peaked either at the *vertex* (Fig. 3.), in the *parietal* region (Fig. 4), or successively at the vertex and then postcentrally (*mixed* pattern, Fig. 5). Positive components were preceded by a negative component that peaked at the vertex (Fig. 3 lower) or postcentrally (Fig. 3 upper and Fig. 5 upper). Parietal positive peaks were sometimes preceded by three successive parietal waves (negative-positive-negative) of short duration (Fig. 4 upper). Topographical patterns of emitted potentials varied in the same subject from trial to trial. The relationship of emitted potentials to the task could not be clearly established, although the vertex negative-vertex positive pattern tended to occur within the initial five or six omission trials of a run.

Preliminary measurement of amplitude and latency parameters in the single-trial maps of two subjects (166 maps) indicated that: (1) the latency of the vertex positive component ($\bar{x}$ = 374 msec, S.D. = 87 msec) was shorter than the latency of the parietal positive component ($\bar{x}$ = 467 msec, S.D. = 92 msec); (2) the latency of negative and positive emitted components increased across runs, regardless of topography; (3) reaction time also increased across runs in the go condition; (4) the first positive peak always occurred before the motor act ($\bar{x}$ interval = 128 msec, S.D. = 78 msec) and was highly correlated with RT (0.77); and (5) the positive component of the vertex negative-vertex positive pattern exhibited higher amplitude ($\bar{x}$ = 17.6 μV, S.D. = 5.4 μV) than the positive parietal component ($\bar{x}$ = 11.2 μV, S.D. = 4.3 μV).

Discussion

Averaged as well as single-trial spatiotemporal maps suggest that the emitted potential following an omitted stimulus is not a unitary phenomenon, but consists of at least two components of different polarity, which seem to reflect different brain activities. Two different patterns of emitted potentials may be distinguished in terms of chronotopographical organization. One pattern is characterized by a positive vertex component (sometimes preceded by a vertex negative component). The other pattern is similar to the association cortex potential (ACP) described by Ritter et al. (1972) and is made up of two parietal components, one negative and the other positive. Both patterns of emitted potentials can be observed during the same task and both can occur together in a single trial, yielding a complex, mixed pattern.

The averaged negative component of the emitted potential to omitted visual stimuli was observed in the parieto-occipital region posterior to the positive component. Simson et al. (1976) showed that the negative component of the emitted potential changed topography when omissions occurred within a series of visual or auditory stimuli, a finding that suggested modality specificity. In the present study, a contralateral negative component was observed in the average maps of three subjects whenever omissions occurred within a series of half-field stimulations, whereas the positive component remained symmetrical. This finding is consistent with the modality-specific character of the negative component reported by Simson et al. However, more information concerning the topographical organization of this component in single-trial data for missing half-field stimuli is needed before drawing conclusions.

During whole-field stimulation, the transverse montage of four subjects showed an asymmetrical negative component larger in the right hemisphere, whereas the positive component was symmetrically distributed, suggesting that the negative and positive components are independent. This right asymmetry is difficult to explain because, with the exception of one subject, the visual evoked potential in full-field stimulation always appeared symmetrical when recorded with the same montage. Since the right hemisphere is known to be active during spatio-visual processing, this asymmetry could be related to the spatial visualisation (visual memory) demands of a task that requires counting, motor response, or withdrawal of motor response in the absence of a visual pattern. Experiments employing verbal rather than visual stimuli are needed for better understanding of the negative component of the emitted potential.

Trial-by-trial analysis did permit differentiation (on the basis of topographical criteria) of several patterns of emitted response during the same task. These topographical patterns seem to reflect different psychophysiological mechanisms that may play a role dependent on the task (cf. Renault et al. in press). Amplitude of the negative component was larger during both go and no-go tasks compared to the counting task. This result may be due to a larger slow negative wave, reflecting a more important preparatory process when a motor response is required.

The pattern consisting of two vertex components (negative and positive) may not be a true emitted potential as described by Weinberg (1970) or Simson et al. (1976) since it is not preceded by a negative modality-specific wave in the parieto-occipital region. This pattern resembles the classical vertex potential described long ago by P. Davis (1939), Bancaud et al. (1953), and Gastaut (1953) and may constitute an orienting response since it decreases with the passage of time, an effect which may reflect habituation. The positive component of this vertex potential seems similar to the P300 evoked by novel stimuli (Courchesne et al. 1975). Consistent with Courchesne's findings, the vertex positive peak in this study was of shorter latency and higher amplitude than the parietal positive peak. The vertex positive component preceded by a parieto-occipital negativity, however, seems to constitute a proper emitted response. This pattern does not seem to habituate with time, is lower in amplitude, and is longer in latency than the pure vertex pattern, suggesting that a more complex mechanism, possibly related to time estimation, is involved.

According to Squires et al. (1975) and to Ford et al. (1976), the positive component of the emitted response has a centroparietal distribution when attention is involved, whereas it peaks in centrofrontal regions when attention is not required. Attention was not manipulated in these experiments, so this hypothesis cannot be directly evaluated. Nevertheless, the topographical similarity between the pure parietal pattern and the visual evoked potential suggests that the negative component of the emitted potential may reflect a sensory information retrieval mechanism (Weinberg et al. 1970, 1974; John 1972), thus involving attention processes and acting as a feedback control on perception. When a sequence of frontocentral and parietal positive waves occur in the same trial, the two components may reflect two distinct stages in a complex decision process, separated in time by approximately 100 msec.

Summary

The chronotopographical organization of the emitted potential to expected, but missing, visual stimuli was studied in five subjects. Three runs of 450 whole-field visual stimuli were presented in which a random 10% of the stimuli were omitted. Three task conditions were used: (1) counting omissions, (2) motor response to omissions (go), and (3) motor response to visual stimuli but not to omissions (no-go). Left half-field and right half-field stimuli were also used in a second study. Data were displayed in both averaged and single-trial spatiotemporal maps.

Results indicate that the emitted potential consists of at least two components, a negative modality-specific wave that peaks in the parieto-occipital region and a positive wave that peaks either centrally or postcentrally. A complex pattern including two positive waves peaking in different regions was also observed. When negative and positive components both peaked at the vertex, the pattern was interpreted as an orienting response rather than emitted potential. Emitted potentials were discussed as indices of complex decision mechanisms involving time and sensory information retrieval.

AUDITORY EVOKED POTENTIALS, SKIN CONDUCTANCE RESPONSE, EYE MOVEMENT, AND REACTION TIME IN AN ORIENTING RESPONSE PARADIGM[1]

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Unpredictable stimulus events sometimes elicit a complex of reactions called the orienting response (OR). Ritter et al. (1968) were the first to suggest that a late positive component (P300 or P3) of the evoked potential (EP) was also a component of the OR, and we have pursued this theme in a series of papers (Roth 1973, Roth and Kopell 1973, Ford et al. 1976). Both the amplitude of P3 and the amplitudes of other OR components are inverse functions of stimulus probability (Tueting et al. 1970, Roth 1973, Sokolov 1963). Both P3 and other OR components can occur in the absence of instructions that make the eliciting stimuli task-relevant (Roth 1973, N. K. Squires et al. 1975), but both increase in mean amplitude when such instructions are given (Picton and Hillyard 1974, Sokolov 1963, Bernstein et al. 1975). Task-relevance is usually assumed to influence some part of the attention process.

The primary purpose of this study was to determine the relationship between the skin conductance response (SCR) and the auditory evoked potential (AEP) in an OR paradigm. SCR has often been used as an indicator of the OR (Raskin 1973). We hypothesized that, since both P3s and SCRs may be components of the OR, larger SCRs would be associated with larger P3s. In addition, we wanted to examine critically the relationship between eye movement and the AEP. If eye movements or blinks are sometimes components of the OR (as they are of the closely related startle or defensive response), one would also expect more eye movement to be associated with larger P3s. Finally, we wanted to examine the relationship between reaction time (RT) and AEPs.

To test these relationships, we sorted individual trials as to whether they were above or below a criterion level for SCR, eye movement, and RT. A special feature of our sorting procedure was that it would not accept consecutive trials above (high trials) or below (low trials) the criterion level. Instead, high and low trials were selected alternately, a procedure that yielded high and low AEP averages from comparable points in time. Without this restriction, high trials for a given variable might be selected from the beginning of a run and low trials from the end. Roth (1973) and Raskin et al. (1969) have previously shown that P3 amplitude and SCR amplitude decline over time if the eliciting stimuli are task-relevant. Our sorting procedure allowed us to control for the effect of time and thus to look for relationships between variables that are independent of time.

Task-irrelevant stimuli of moderate or low intensity elicit SCRs that habituate to an asymptote very close to zero after 3 to 20 repetitions. In order to obtain an adequate number of trials with stimulus-specific SCRs for EP averaging, we used a 95-dB SPL musical chord as a stimulus. Stimuli of this intensity persist in eliciting SCRs at least intermittently (Raskin et al. 1969).

Method

Eight male and eight female subjects with a mean age of 25 years participated in a single 3-hr session.

The electroencephalogram (EEG) was recorded from subdermal pin electrodes at Fz, Cz, and Pz referenced to linked disc electrodes attached to the earlobes. The electrooculogram (EOG) was recorded from disc electrodes applied 3.5 cm above and 2.0 cm below the pupil of the right eye. EEG and EOG were amplified and recorded with a system set to a bandpass of 0.03 to 100 Hz (3dB points of 6 dB/octave rolloff curves). The amplifiers have an input impedance of 100 megohms at these settings. Skin conductance level (SCL) and skin conductance response (SCR) were recorded from a single pair of 7.5-mm-diameter disc electrodes applied to the palmar surface of digits 2 and 3 of the nondominant hand. Skin conductance was transduced by a device that applies a constant 1.0 volt across the electrodes and has as its output a voltage proportional to skin conductance.

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[1] This research was supported by NIMH Grant DA 00854 and the Veterans Administration

Before stimulation, each subject opened and closed his eyes to allow quantification of eye artifact at each EEG lead.

Two types of auditory stimuli were presented binaurally through earphones. Each type was controlled by electronic switches set to rise and fall times of 2.5 msec and to a duration of 50 msec. One stimulus was a 95-dB SPL chord consisting of 550-, 900-, and 1080-Hz tones. Interstimulus intervals (ISIs) between chords were multiples of a 1-sec interval and followed a fixed pseudorandom sequence based on a Bernoulli distribution. The probability of a chord occurring after any 1-sec interval was 0.1. In two of the four stimulation periods, chords were the only type of stimulus presented (no-background conditions). In the other two stimulation periods, a 65-dB noise burst was presented at 1-sec intervals (background conditions). At the same ISIs as in the no-background conditions, the 65-dB noise burst was replaced by a chord. During both conditions, a 50-dB white noise background was used to conceal extraneous sounds.

Instruction conditions were also varied. In press conditions, subjects were told to press a button as quickly as possible whenever they heard a chord. In read conditions, subjects were told to read a popular mystery novel and to ignore all sounds. Each subject received the four possible combinations of stimulus and instruction conditions in four runs counterbalanced in order across subjects. Each run lasted about 20 minutes, during which time 65 chords were presented. After each run, there was a brief rest period.

The value of the SCR for each trial was calculated as the sum of absolute deviations between a prestimulus baseline and the skin conductance over an interval from 2.4 to 6.4 sec after the chord. Sampling occurred every 5 msec. Such a sum is closely proportional to the integral of the absolute deviation over the interval. EOG deviation was calculated similarly over the interval from 2 to 420 msec. Trials with RTs more than 770 msec were excluded.

The criterion levels were the mean RT across all trials of a run for RT sorting, the mean EOG deviation across all trials of a run for EOG sorting, and 70% of the mean SCR across all trials of a run for SCR sorting. Criterion levels were established separately for each run of each subject. Since the sorting algorithm required high and low trials to alternate–i.e., after selection of a high or low trial, subsequent high or low trials were bypassed until a trial of the opposite type was found–the number of averages for a given AEP depended on the time course of the criterion variable. Pilot studies indicated that the criterion level of mean EOG and mean RT provided an adequate number of both high and low trials for AEPs. Mean SCR, however, did not provide enough high and low trials, so that 70% of the mean SCR was used as the criterion level. Data from each EEG and EOG channel were sorted into six different categories (high/low SCR, high/low EOG, and high/low RT) and averaged over a 420-msec epoch. Whether the initial trial in the average was high or low was balanced across conditions.

EP averages were corrected for eye movement artifact by subtracting a predetermined percentage of the EOG average from each EEG average. These percentages varied across load and subject.

Peak amplitudes and latencies were measured by finding the minimum or maximum amplitude in fixed latency ranges and subtracting a prestimulus baseline from these points. On the basis of visual inspection of individual AEPs, peak latency criteria were defined that would be valid for the greatest number of curves. These criteria were as follows: N1, 70-140 msec; P2, 150-230 msec; N2, 200-300 msec; and P3, 250-380 msec. Fixed latency ranges allow replicability between laboratories, but are not entirely satisfactory. For example, one subject's first prominent negative peak occurred at 180 msec under certain conditions. In certain AEPs from several subjects, it was unclear whether the prominent positive peak should be considered a late P2 or an early P3. N2s were particularly inconsistent and appeared to depend on the amplitudes and latencies of the surrounding positive peaks.

Trials picked by the three criterion variables were largely independent. The mean number of averages for all sorts was 11; the mean overlap between trials picked for both SCR and RT sorts was 1.7 trials, between SCR and EOG, it was 2.0, and between EOG and RT, it was 2.2.

A repeated measures of variance was used for statistical evaluation of results. Results reported below are significant at $p < .05$.

Results

Fig. 1 shows grand averages across all subjects of vertex AEPs sorted by SCR and RT. N1 peaks are more prominent in the no-background conditions, while P3 peaks are more prominent in the background conditions, especially when a button press was required. Fast RTs are associated with larger P3s in the

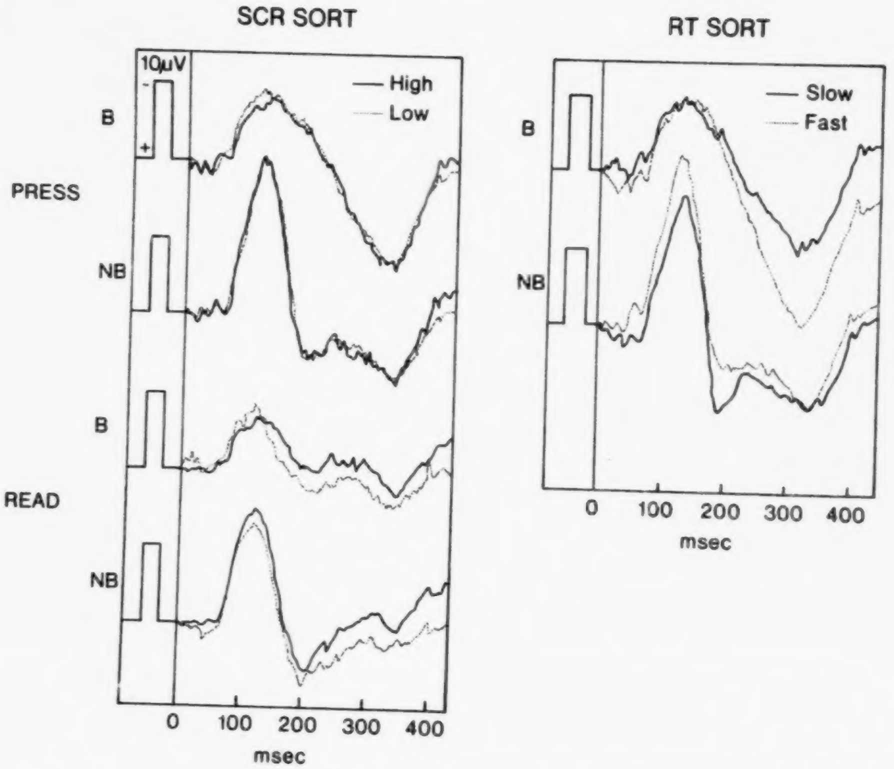

Fig. 1. AEPs sorted by skin conductance response (SCR) and reaction time (RT) combined over 16 subjects. Only Cz is illustrated. B = background; NB = no background.

background condition. In read conditions, AEPs beginning from about 100-200 msec are more positive in the low than in the high SCR trials.

Fig. 2D presents the mean SCR and RT criterion variables for trials selected by the sorting procedure in various conditions. SCRs were smaller in press than in read conditions for high SCR trials. SCLs (not illustrated) preceding high SCR trials were not different from SCLs preceding low SCR trials. Table 1 provides data for comparing means of sorted trials with means and within-subject standard deviations (SDs) over all trials.

Fig. 2A, 2B, and 2C present mean N1 and P3 amplitudes for each of the sorts. Background, lead, and attention effects were generally the same regardless of the method of sorting. These effects are summarized below.

Background. N1 was larger for all sorts in no-background conditions. Although there was a consistent interaction between background and lead, this background effect was significant at each lead. For the EOG and RT sorts, N1 was later in no-background conditions. Neither P2 nor N2 were affected by background. P3 was later in background conditions for SCR and EOG sorts.

Lead. N1, P2, N2, and P3 amplitude consistently showed main lead effects. N1 was largest at Cz, P2 and P3 were largest at Pz, and N2 was largest at Fz. N1, P2, and P3 latencies also consistently showed main lead effects. N1 was earliest at Pz, and P2 and P3 were earliest at Fz.

Attention. N1 amplitude was smaller during read than during press in the SCR sort, and it was earlier during read than during press in the SCR and EOG sorts. P2 amplitude showed no attention effect, but P2 latency was consistently earlier during read than during press. N2 amplitude was also unaffected by attention, but N2 latency was earlier during press than during read. P3 amplitude was consistently larger during press than during read. An attention x lead interaction appeared to be due to the attention effect, being strongest at Pz. P3 latency was unaffected by attention.

High/low SCR. The only effect of this factor was on P3 amplitude, which showed a significant attention x high/low interaction. Low SCRs were associated

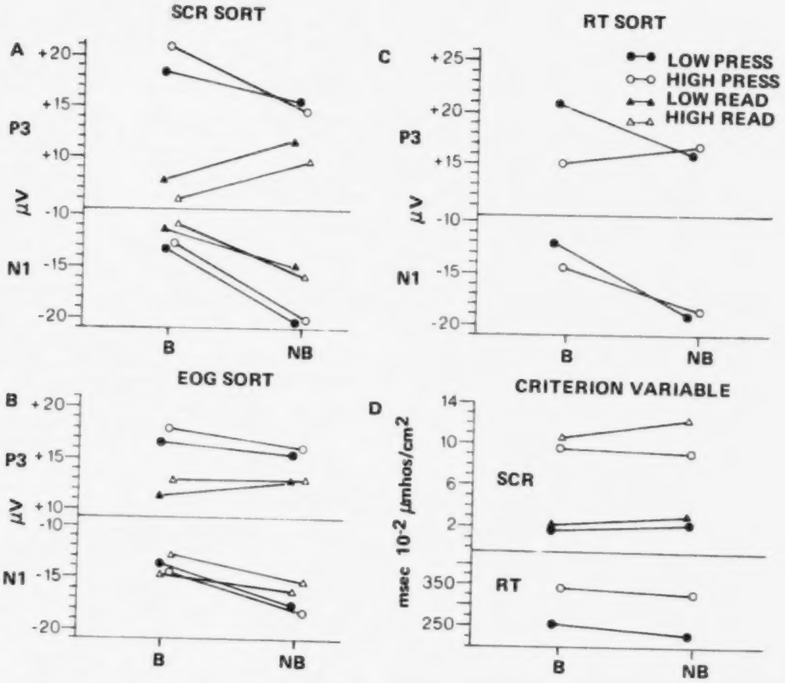

Fig. 2. A-C: Mean P3 and N1 amplitude across all leads and subjects for each condition sorted by skin conductance response (SCR), electrooculogram (EOG) and reaction time (RT). D: Mean values for SCR and RT criterion variables when sorted by SCR and RT, respectively. In A-D, low = low SCR, low EOG voltage, or fast RT.

Table 1. Mean Over All Trials, Mean Within-Subject Standard Deviation (SD) Over All Trials, Mean of High Trials, and Mean of Low Trials for the Three Criterion Variables

		Background		No background	
		Press	No press	Press	No Press
SCR, μmhos/cm^2 x 10^{-2}	Mean	6.269	7.393	6.911	8.050
	Mean SD	6.832	7.932	6.705	7.880
	Mean high	9.553	11.711	8.785	12.525
	Mean low	1.646	1.762	1.874	2.250
EOG, arbitrary units	Mean	90	36	93	38
	Mean SD	63	19	59	17
	Mean high	214	127	224	120
	Mean low	34	17	31	16
RT, msec	Mean	287		261	
	Mean SD	72		59	
	Mean high	342		354	
	Mean low	248		225	

with large P3s only during read conditions. This effect is small, with mean differences about 2 μV.

High/low EOG. No amplitude or latency effects were present.

High/low RT. For both P2 and P3 amplitudes, large peaks were associated with fast RTs, but only in the background condition. N2 latency was earlier when RTs were fast.

Discussion

Contrary to the initial hypotheses, no evidence of a positive association between AEP peaks and SCR or EOG was found. The AEP was affected, however, by background and attention parameters. The effects of these parameters on N1, P2, and P3 were similar to effects observed previously (Hillyard et al. 1973, Picton and Hillyard 1974, Roth et al. 1976, Ford et al. 1976b). There was some evidence that either P2 and P3 were not completely separated by the latency criteria or a single positive process was present at both latency ranges. Both P2 and P3 were largest at Pz, whereas P2 would be expected to be largest at Cz (cf. Roth et al. 1976).

The effects of RT sorting on P3 amplitude in the background condition may also be an attention effect, since fluctuation in RT may occur with fluctuation in attention. Similar findings were reported by Karlin et al. (1971). It is unlikely that the 7 μV P3 difference between fast and slow RT averages is explainable on the basis of EPs to the motor response itself. The relevant components of the finger movement potential have a mean peak-to-peak amplitude of only 3 μV, even when averaging is response-synchronized (Deecke et al. 1976). A readiness potential would not be present to a significant degree since the subject is performing an unwarned RT task. If the effect of RT sorting is based on attention, the absence of this effect in the no-background condition is puzzling. It is also possible that P3 latency jitter plays a role in the RT sorting effect.

There are several possibilities why our hypotheses were not confirmed. Because of the intensity of the stimuli, a defense response may have been elicited instead of an OR. The OR and defense response are both accompanied by SCRs and eye movements; however, the OR is associated with increased sensitivity to stimuli and the defense response may be associated with decreased sensitivity (Sokolov 1963; Loveless, this volume). Defense responses, however, are supposed to be resistant to habituation, whereas in this study SCRs or eye movements tended to decrease after the first few occurrences of the chord. This leads to a second possibility, namely, that intermittant SCRs and eye movements were habituated ORs that have different correlates than the initial ORs. Evidence from other experiments indicates that this can be the case for the SCR (Siddle 1974). In addition, some SCRs or eye movements might have occurred spontaneously, following the chords only by coincidence. A third possibility is that eye movements, SCRs, and P3s are indeed components of the OR, but that they have only low positive correlations, which disappear when the effect of time is removed.

The grand averages in Fig. 1 suggest that the inverse association between P3 and SCR amplitudes in the read conditions may be the result of a slow potential shift. Several such shifts have been described (Loveless and Sanford 1974, Näätänen 1975, N. K. Squires et al. 1975, Roth et al. 1976). One could hypothesize that there is a negative slow potential OR component, although the lack of OR-related changes in N1, P2, or N2 amplitude or distribution or in P3 distribution makes that possibility tenuous. It is unclear why SCR sorting had an effect only in the read conditions, unless the motor response somehow altered the properties of P3 or the SCR. Although one would expect motor response to increase SCRs in general, high SCR trials had larger SCRs in the read rather than press condition.

The negative result for EOG sorting serves as a rationale for continuing to eliminate eyeblink-contaminated trials in order to control for the spread of potentials generated by the eyes. There was no association between potentials in the EOG and the EEG besides this artifactual one, which was minimized by our correction procedure. Of course, this rationale is only valid when experimental parameters similar to ours are used.

This experiment is not the final word on the relationship between P3 and non-EEG orienting response components. Our suggestions as to why our hypothesis was not confirmed should be taken as suggestions for new experiments. We think that an artificial gap has arisen between the older autonomic psychophysiology and the newer EP psychophysiology, and that the simultaneous use of autonomic and EEG variables can lead to a fruitful integration of the two areas in the future.

Summary

Auditory evoked potentials (AEPs) to a pseudorandom series of 50 msec, 95-dB chords were studied in 16 subjects. The electro-oculogram (EOG) and skin conductance response (SCR) were also recorded. There were four runs with either chords alone (no background) or chords inserted in a train of 50-msec, 65-dB noise bursts (background). Subjects were required either to read or to press a reaction time (RT) button to the chords. In all conditions, the chords

had a 0.1 probability of occurrence in any 1-sec interval.

AEPs were obtained by sorting individual trials by high/low SCR, high/low EOG, and high/low RT. The sorting was based on the mean of the sorting variable for individual runs, and required high and low trials to alternate.

Large SCRs were associated with small P3s during the read conditions. This effect is apparently not due to changes in amplitude of the classical P3 wave, but is a result of changes in positive or negative slow potential processes. Fast RTs were associated with large P2s and P3s when background tones were present. Many previously observed findings concerning N1, P2, and P3 were replicated.

Acknowledgments

We thank S. J. Lewis, M. J. Rosenbloom, and M. T. Chargin who assisted in this study.

SEQUENTIAL DEPENDENCIES OF THE WAVEFORM OF THE EVENT-RELATED POTENTIAL: A PRELIMINARY REPORT[1]

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One basic assumption underlying research involving the average event-related potential (ERP) is that when stimulus and task variables are held constant, ERPs elicited by all occurrences of a particular event are identical. As the number of variables shown to influence the ERP continues to increase, investigators have resorted to increasingly sophisticated methods for creating averaged ERPs from presumably homogenous populations of single-trial waveforms. One popular technique has been to randomize the order of stimulus presentation to eliminate differential preparedness (Näätänen 1970) and to segregate trials for averaging according to which stimulus was presented on each trial. Studies using this paradigm have contributed significantly to our understanding of the effects of attentional variables, task requirements, stimulus relevance, and stimulus probability (e.g., Donchin and Cohen 1967, Ford et al. 1973, Harter and Salmon 1972, Picton and Hillyard 1974, Ritter and Vaughan 1969, Rohrbaugh et al. 1974, Ruchkin and Sutton 1973, N. Squires et al. 1975, Sutton et al. 1965, Tueting et al. 1970, and Wilkinson and Lee 1972).

A recent study by Squires and Donchin (1976), however, suggests the need to reassess this assumption. The standard method of segregating trials for averaging was supplemented by categorization of ERP waveforms according to waveform statistics generated on each trial. Wide variations in averaged ERP were found for events often considered identical, and close inspection of waveform statistics suggested that variations were at least partly due to effects of the sequence of stimulus presentations. This explanation seemed plausible in view of reports by Remington (1969) and others (Falmagne et al. 1975) showing that choice reaction time, which has often been linked to the P300, is exquisitely sensitive to the specific sequence of preceding trials. Since the existence of such sequential dependencies would violate the fundamental assumption that ERPs under the conditions described can be considered identical, an investigation was designed to parallel the reaction time study of Remington (1969).

Method

Seven subjects listened to series of tone bursts (60 msec, 60 dB SPL) presented at a rate of one every 1300 msec. On each presentation the tone was either high pitched (1500 Hz) or low pitched (1000 Hz) with equal probability (P = 0.5). Subjects counted the occurrences of the high-pitch tone. In a second experimental condition, everything remained the same except that stimulus probabilities were changed to 0.3 (high pitch) and 0.7 (low pitch).

EEG was recorded from electrodes at Fz, Cz, and Pz referred to linked mastoids with a wrist ground. The bandpass of the amplifying system was set for a time constant of 0.8 sec with an upper half-amplitude frequency of 35 Hz. A 768-msec epoch of EEG, beginning 100 msec prior to stimulus onset, was digitized on each trial and stored for later analysis. Additional electrodes were situated to record eye-movement and blink potentials. EEG epochs with eye-related artifacts were excluded from the waveform analysis, but all trials entered into the tabulation of stimulus sequence.

Results and discussion

One subject's ERPs (Cz) to the counted high-pitch tones (P = 0.5) are shown in Fig. 1. The terminology of Remington (1969) has been used. An "A" represents the stimulus trial n (here the high-pitch tone). Thus the ERP for the first-order sequence (A) represents the average from all presentations of the high-pitch tone. There were two possible patterns for second-order sequences, "AA" and "B." The ERP for "AA" was formed from trials on which a high-pitch tone was preceded by a high-pitch tone, and the "BA"

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[1] This research was supported by the Advanced Research Projects Agency of the Department of Defense under Contract No. DAHC 15 73 C 0318 and Contract No. ONR US NAVY N-000-14-76-C-0002, both to E. Donchin.

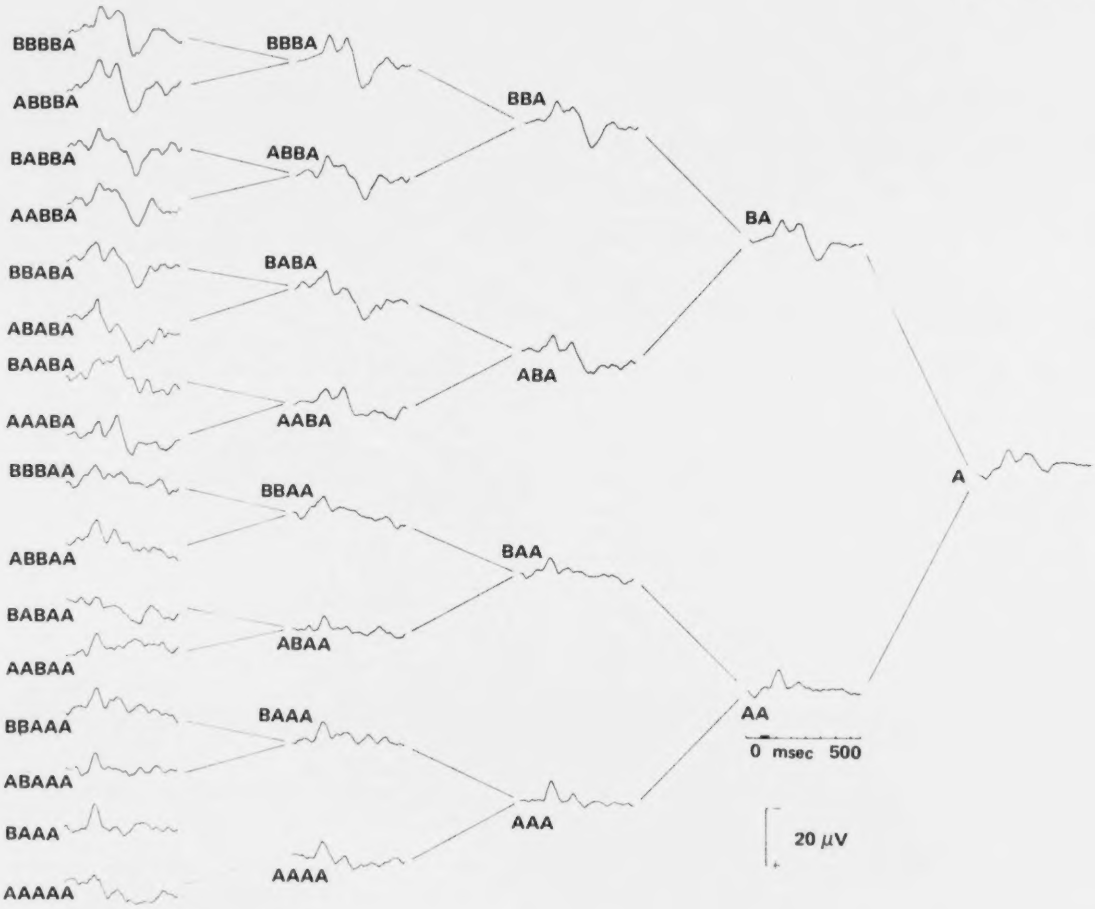

Fig. 1. Average ERP waveforms of one subject for different stimulus sequences. "A" and "B" represent occurrences of the high- and low-pitched tones, respectively. ERPs in each case are elicited by the final high-pitched tone in the designated sequence.

ERP from high-tone trials preceded by low-tone trials. Similarly, there were four third-order patterns, 8 fourth-order patterns, and 16 fifth-order patterns.

In Fig. 1, waveforms are presented at nodes of a tree structure. A similar tree was shown by Remington to be useful in organizing reaction time data. Remington derived the tree from a repetition hypothesis, according to which the addition of a like stimulus (A) in front of a sequence leads to a shorter reaction time to stimulus A on trial n than the addition of an unlike stimulus (B).

There is a systematic variation in the ERP waveform elicited by high-pitch tones as a function of the sequence of preceding stimuli. Examination of the upper and lower limbs of the tree structure shows that the amplitude of the P300 component (along with the associated N200 and slow wave components) (K. Squires et al., (1977); N. Squires et al. 1975) increases with increasing numbers of unlike stimuli preceding the eliciting stimulus and decreases with increasingly long runs of like stimuli. No systematic shifts in latencies of waveform peaks were noted. Remington's reaction time data, however, suggest that latency shifts are likely to be rather small (a maximum of about 20 msec between the "A" and "BBBBA" sequences); peak-latency shifts of this magnitude are beyond the resolution of the techniques used in this study.

Within each order (i.e., within sequences of equal numbers of stimuli), there were systematic variations in waveform that were independent of the absolute number of like and unlike stimuli within the short sequence (cf. waveforms for "ABBBA" and "BBBAA"), but were critically dependent upon where in the sequence the As and Bs appeared and

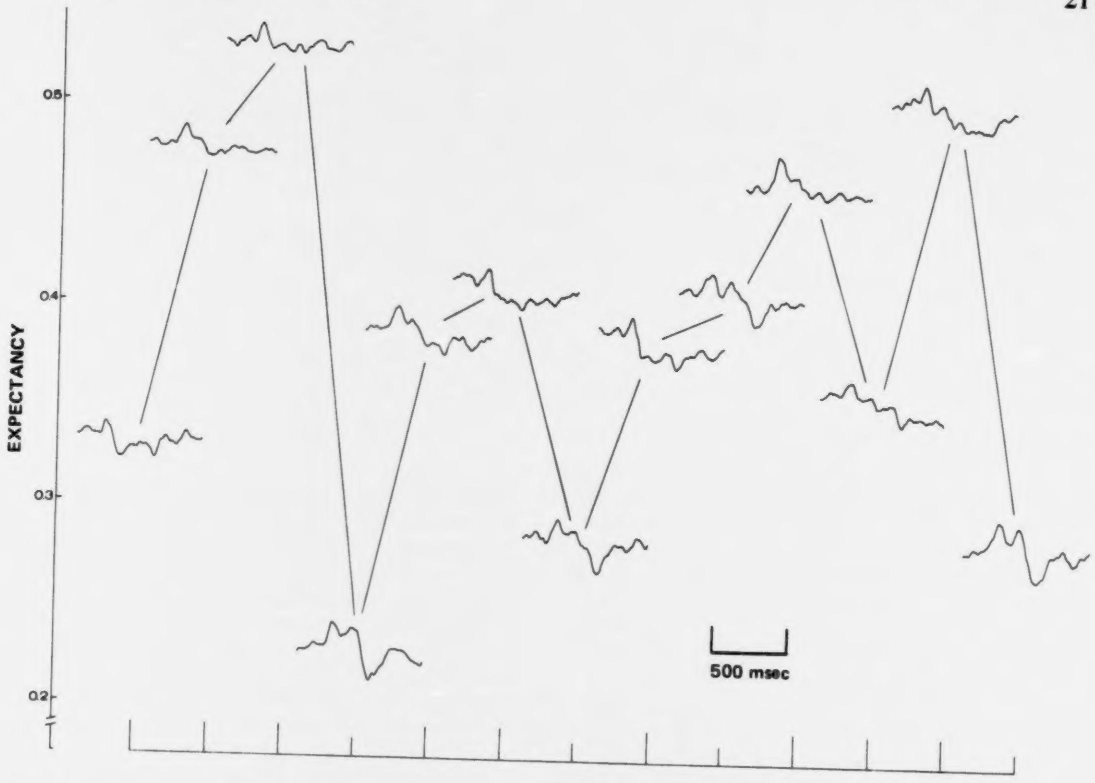

Fig. 2. Expectancy for the stimulus on each trial in a sequence of trials along with the average ERP waveforms for the corresponding sequence (same subject as Fig. 1). High-pitched and low-pitched tones represented by short- and long-stimulus markers, respectively.

whether or not patterns (e.g., alterations) emerged. A detailed analysis of waveform variations is presented elsewhere (K. Squires et al. 1976).

To summarize, a model for predicting waveform statistics based upon the concept of expectancy has been developed. The model assumes that the expectancy for each stimulus is determined by three factors: (1) the memory for event frequency within the prior stimulus sequence (an exponentially decaying function of position within the sequence), (2) the specific structure of the sequence (whether patterns of alternations are set up), and (3) the global probability of the stimulus. According to the model, the amplitude of the complex of late components (N200, P300, and slow wave) increases as the expectancy for the presented stimulus decreases. The regression equation based upon the mean data for seven subjects at stimulus probabilities of 0.3, 0.5, and 0.7 accounted for 78% of the variance in the statistical data.

Fig. 2 illustrates the dynamic nature of changes in expectancy from trial-to-trial and the corresponding effect on the ERP waveform. These results show that the ERP waveform is remarkably sensitive to trial-to-trial variations in the sequence of events preceding the eliciting event, and provide new evidence for the association of late ERP components with subtle cognitive processes. These results also suggest that before we can assume homogeneity of events associated with the average ERP, more sophisticated groupings of single-trial waveforms than have previously been utilized must be developed.

Summary

Subjects counted one of two auditory stimuli that occurred in a Bernoulli sequence. Event-related potentials (ERPs) were averaged for each stimulus according to the sequence of preceding stimuli. Late ERP components decreased in amplitude with increasing numbers of like stimuli and increased in amplitude with increasing numbers of unlike stimuli within the preceding sequence. This effect was found to extend as far back as trial N-5. It was concluded that these variations in amplitude of late components were related to variations in the subject's expectancy for a stimulus.

FUNCTIONAL EQUIVALENCE OF SIGNAL-PRESENT, SIGNAL-ABSENT, AND THRESHOLD-DETECT P3s[1]

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The omission of a highly expected stimulus has been shown to elicit a positive wave recordable from the human scalp, with a latency of over 300 msec. This late-positive component can be obtained by omission of stimuli in several modalities, including auditory (Sutton et al. 1967; Picton et al. 1974; Ruchkin et al. 1975; Ruchkin and Sutton, in press, a,b), visual (Barlow 1969; Ruchkin and Sutton 1973, in press), and tactile (Klinke et al. 1968). These results have frequently been interpreted in terms of the delivery of information; the omission of a stimulus elicits a late-positive component when that omission carries task-relevant information, for example, when the omission is a target to be counted (Picton et al. 1974, Barlow 1969) or confirms or disconfirms a prior guess (Sutton et al. 1967; Ruchkin and Sutton 1973, in press a,b). Within this framework, the late-positive component to omitted stimuli may be a manifestation of the same process that underlies the P3 component that follows the reception of target stimuli in a number of paradigms (cf. K. Squires et al. 1973a and Hillyard and Picton, in press, for reviews). Ruchkin et al. (1975) have provided support for this conjecture by demonstrating that the probability of event occurrence has similar effects on the amplitudes of the late-positive components associated with stimulus presence and stimulus absence. Moreover, Ritter et al. (in press) have found that the scalp topography of the P3 elicited by omissions from an ongoing train (either auditory or visual) is indistinguishable from that elicited by intramodality targets embedded in the same train.

Under slightly different circumstances, i.e., when subjects are required to judge the presence or absence of a near-threshold tone pip, there is considerable evidence showing that signal-absence does not readily elicit a late-positive component (Hillyard et al. 1971, Paul and Sutton 1972, K. Squires et al. 1973b, K. Squires et al. 1975a), despite the fact that stimulus absence certainly carries task-relevant information in this paradigm. The following experiments were designed to reconcile these results by systematically varying three important variables that differentiate the previously described paradigms and that alone, or in some combination, might account for the discrepancies noted: the probability of signal presentation, the intensity of the signal, and the manner of signal presentation, whether on a trial-by-trial basis or in an ongoing train. Measurement of the scalp distribution of the late components was also included in this study to provide a further basis for comparison.

Methods

Five adults with normal hearing, including authors KS and NS, served as subjects in a series of 15 to 20 two-hour sessions.

Evoked potentials to all events were recorded from frontal, vertex, and parietal midline sites (25%, 50%, and 75% of the inion-nasion distance, respectively), using Ag/AgCl disc electrodes referred to right mastoid. Vertical EOG was recorded and averaged in all subjects to rule out contamination from ocular artifacts. The half-amplitude frequency bandpass of amplifiers was set at 0.15 to 500 Hz.

During the experiment, the subject sat in a reclining chair in an acoustically shielded chamber with a panel of lights and response buttons in front of him or her. In the first experiment, the subjects reported on a trial-by-trial basis whether or not a signal had occurred. Each trial began with a warning tone (S1), which was a binaural 1-kHz, 50-msec tone burst, at an intensity of 65 dB SPL, presented against a continuous background of white noise (65 dB SPL). After an interval of 600 msec, from the onset of the warning tone, a second 50-msec, 1 kHz tone (S2) occurred with a certain probability (0.9, 0.5, or 0.1 on different blocks of trials). The intensity of S2 was also varied across blocks–90 dB (SPL), 65 dB (SPL), or threshold level. Threshold intensity was determined individually for each subject by the method of constant stimuli so that each subject's detection performance was 90 to 95% correct. This intensity was 44 dB SPL for most subjects. Thus, there were nine stimulus configurations, three S2 intensities at three *a priori* probabilities. Following each trial, a small neon bulb was lighted 1600 msec after the onset of S1 to request a response of the subject. Two response buttons were available, one to indicate that S2 had been presented and the other that S2 had not been presented. The time from the response-light presentation to the beginning of the next trial varied randomly from 1500 msec to 3500 msec. There were 100 trials per block, all under one condition of stimulus intensity and probability. Experimental conditions were presented first in order of decreasing probability of a signal occurrence, with decreasing intensity within each probability, and then the entire sequence was repeated in the reverse order. Completion of an entire sequence required 3 to 4 hours.

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[1] This research was supported by NASA Grant NGR 05-009-198 to Robert Galambos and NIH Grants NH 25594 to S. Hillyard and NS 07454 to Donald Norman, who provided the experimental facilities.

Evoked response recording began 100 msec before the warning tone and continued until 750 msec after the signal, for a total of 1450 msec. Separate averages were made for signal-present and signal-absent trials. Randomization of trials was under the control of a PDP-9 computer, as were evoked-response averaging, signal presentation, and collection of the behavioral response.

Results

A complete set of averaged evoked responses (from the vertex) for subject HC is shown in Fig. 1. Evoked responses from the signal-present trials (solid lines) and from the signal-absent trials (dotted lines) are superimposed. Decreasing S2 probability is from left to right, and decreasing S2 intensity is from top to bottom. The late-positive component evoked by signal omission can be seen at all intensity levels for the S2 probability of 0.9. At each signal intensity the amplitude of this component decreased as the S2 probability decreased. Simultaneously, the P3 to signal presentation increased in amplitude as that signal was made less probable.

The averaged amplitude (re a baseline over the 100-msec interval prior to S2 occurrence or omission) and latency data from all subjects are shown in Fig. 2. Although the amplitude of the signal-absent late-positive component is less than that of the signal-present P3 (Fig. 2A; $F(1, 4) = 9.41$, $p < .05$), and latency is longer (Fig. 2C; $F(1, 4) = 45.46$, $p < .01$), the scalp distributions of the two components are similar (Fig. 2A), both being maximal in amplitude at the parietal

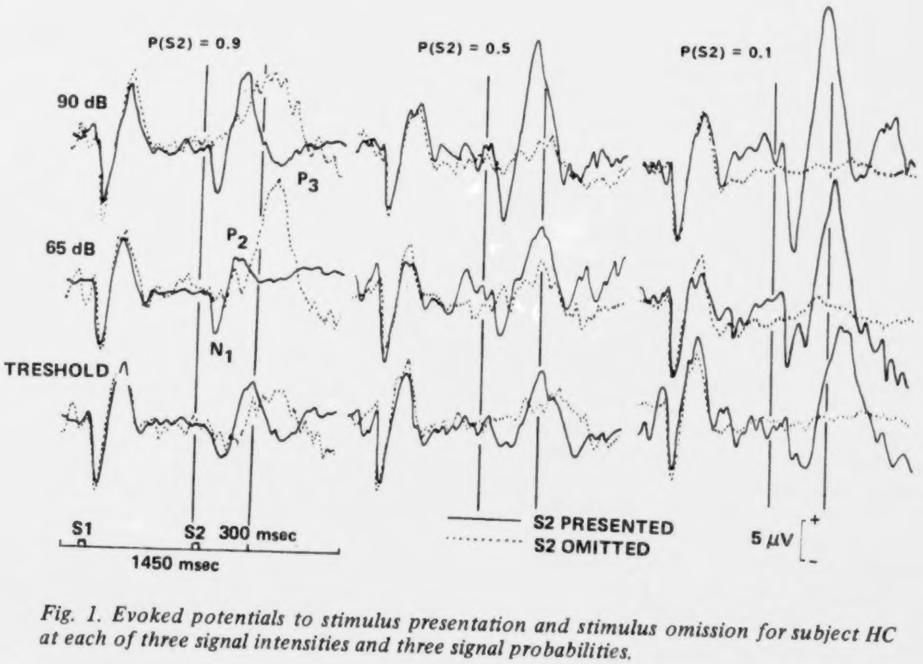

Fig. 1. Evoked potentials to stimulus presentation and stimulus omission for subject HC at each of three signal intensities and three signal probabilities.

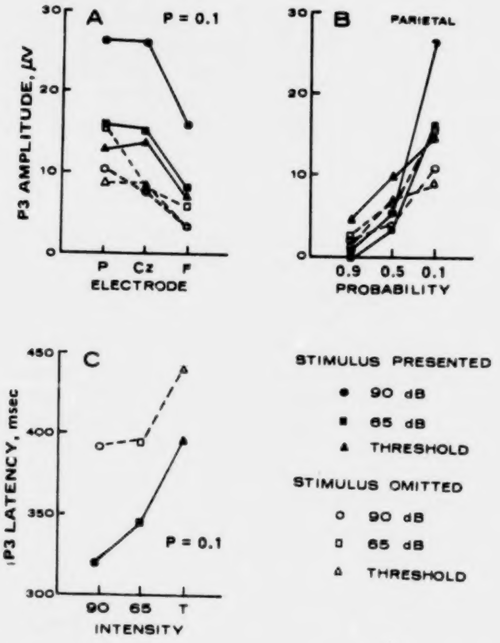

Fig. 2. A. P3 amplitude as a function of electrode location for signal-present and signal-absent evoked potentials at each signal intensity. B. P3 amplitude (parietal electrode) for signal-present and signal-absent at each level of probability of the eliciting event. C. P3 peak latency as a function of signal intensity.

electrode ($F(2, 8) = 6.42$, $p < .05$). The electrode by condition (present-absent) interaction was nonsignificant. Furthermore, both components increased in amplitude as the probability of the eliciting event decreased (Fig. 2B; $F(2, 8) = 8.78$, $p < .01$) and both increased in latency with decreasing signal intensity (Fig. 2C; $F(2, 8) = 10.71$, $p < .01$).

In a second experiment in which stimuli were occasionally omitted from an ongoing train, a late-positive component was also evoked by the stimulus omission, with a parietal-maximum scalp distribution. The vertex waveforms for one subject are shown in Fig. 3. As in the previous experiment, the latency of this component increased as the signal intensity decreased. Furthermore, the scalp topography of P3 to the omitted stimulus was virtually identical to that obtained under similar conditions in the first experiment; the mean amplitudes at the parietal, vertex, and frontal electrodes were 10.2, 7.5 and 3.9 µV, respectively, for the signal level of 90 dB (compare with Fig. 2A, open circles).

Discussion

These data demonstrate a close resemblance between the signal-present and signal-absent late-positive components: scalp distributions are the same, amplitudes of both increase with decreasing probability of the eliciting event, and latencies of both increase with decreasing signal intensity. This latter finding suggests that the timing of the decision as to whether or not a signal has been presented is determined by the loudness of that signal.

While the functional similarity of the signal-absent and signal-present P3s is apparent, the signal-present P3 is consistently earlier and of greater amplitude. This asymmetry between the effectiveness of signal-presence and signal-absence in eliciting P3s has previously been noted by investigators using signal detection paradigms (Hillyard et al. 1971; K. Squires et al. 1973b, 1975a) and guessing paradigms (Sutton et al. 1967; Ruchkin and Sutton, in press a). Ruchkin and Sutton (in press a) have suggested that stimulus omission results in both poorer time-locking of the P3 and in greater equivocation (less *a posteriori* information), and that both of these factors reduce the amplitude of the stimulus-absent P3. In support of this analysis,

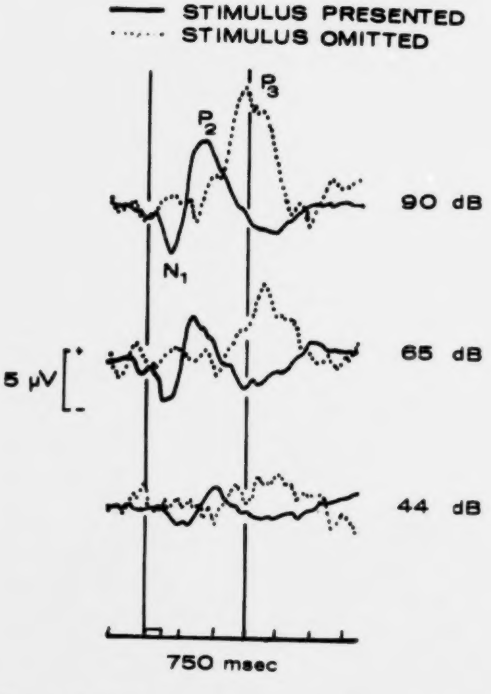

Fig. 3. Evoked potentials to stimulus presentation and stimulus omission for subject KS in the counting procedure where stimulus omission was the infrequent event (P = 0.10) and the target to be counted.

Ruchkin and Sutton showed that correcting for P3 latency variation on a trial-by-trial basis reduces the amplitude differential between stimulus-absent and stimulus-present P3s, but does not eliminate it, suggesting that the individual stimulus-absent P3s are of lower amplitude as well as more variable in time of occurrence. These conclusions are also consistent with the recent findings of K. Squires et al. (1975b) who found that by obtaining better time-locking of the signal-absent P3 with the help of a visual cue during the observation interval, much, but not all, of the asymmetry in the effects of the two types of events is eliminated.

Finally, the similarity of the P3 latency changes and the P3 scalp distributions obtained in the trial-by-trial (signal detection) procedure and the counting procedure suggests that the late-positive components obtained under the two sets of circumstances reflect the same brain process. A similar correspondence between the distributions of the threshold-detection P3 and the omitted-stimulus P3 has been found by Hillyard et al. (in press).

Summary

Comparisons were made among the late-positive waves (P3s) to presented and omitted auditory stimuli in signal detection and counting procedures. Three probabilities of signal presentation were used (0.9, 0.5, and 0.1) at three intensity levels (90 dB, 65 dB, and threshold). The similarities of amplitude, latency, and scalp-distribution variations with intensity and probability support the functional equivalence of the stimulus-present and stimulus-absent P3s, as well as the equivalence of P3s found in signal-detection and counting paradigms.

A CNV REBOUND FUNCTION: PRELIMINARY REPORT[1]

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Contingent negative variation (CNV) is an event-related brain potential that shows optimal development in a constant-foreperiod simple reaction-time task where a first stimulus (S1) serves as a ready signal for a second stimulus (S2) to which a motor response (MR) is required (Walter et al. 1964). In this situation, there is a unitary attention set to prepare for response to S2. When attentiveness to S2 is fractionated by requiring that subjects time-share between the reaction time task and another overlapping task, CNV development is disrupted. For example, CNV amplitude is reduced when a short-term memory task for letters is interpolated between S1 and S2 on each trial (Tecce et al. 1976, 1978). The divided attention set produced in these studies (press quickly to S2 and remember the letters) produced reduction in CNV amplitude and slowing of reaction time. The association of CNV reduction and slow reaction time was interpreted as a CNV distraction effect. The question remains as to whether this effect can be demonstrated by intermixing trials having the short-term memory task for letters and trials not having this memory load. The present study was designed to assess this possibility.

Method

Thirty-six males served as paid volunteers. Their ages ranged from 18 to 26 ($\overline{X} = 21.06$; SD = 2.66). All subjects except two were right-handed. Subjects were screened medically and psychiatrically.

The basic procedure was a constant-foreperiod simple reaction-time paradigm. The preparatory stimulus (Sl) consisted of a brief (0.15 sec) flash of a black "X" (2 cm in height) appearing on a circular patch of dim light (2.5 cm dia). The projector, which stood 144 cm from the floor, was located 1 meter from the subject's eyes at an approximate angle of 25° from the horizontal. S2 was a 1000-Hz tone of approximately 70 dB sound pressure level presented through earphones 1.5 sec after the "X" and terminated by a telegraph key press. The preferred hand was used for keypressing.

There were two experimental conditions: "control" and "50% letters." A control run consisted of 31 trials of S1-S2-motor response, lasting approximately 7 min. Intertrial intervals varied randomly from 8 to 14 sec ($\overline{X} = 11$) within a rectangular distribution of values 1 sec apart. The 50% letters condition was a modification of the Tecce and Scheff (1969) short-term memory paradigm. This condition involved 31 trials randomly presented in two ways—with or without letters. The 16 no-letters trials were identical to those in the control run and involved only the "X" flash, tone, and key press. The 15 letters trials were similar to no-letters trials except that four letters (A, E, I, and O) were spoken within the X-tone interval through an intercom and subjects were required to repeat the letters upon hearing "OK" spoken by the experimenter 1 to 4 sec after the subject's key press. The letters were given in a different randomized sequence on each trial. The first (no-letters) trial was omitted from data analysis. The sequence of test runs was (1) control condition, (2) 50% letters condition, and (3) control condition. This ABA design is suitable where (A) a baseline condition (first phase) is established; (B) a treatment is given; and (A) a recovery test is made (Johnson and Lubin 1972). There was a 6-min rest between test runs.

EEG was recorded from Fz, Cz, and Pz with linked earlobes as reference. EOG was recorded from 3 cm above and 2 cm below the right eye as measured from center to center of pupil and electrode. Electrodes

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were Beckman Ag/AgCl standard (EEG) and miniature (reference and EOG) types. The time constant for EEG and EOG was 8 sec. High-frequency cutoff was 75 Hz (50% amplitude reduction), with 12 dB per octave roll-off. CNV and EOG data were recorded on magnetic tape. Trials with eye movements, premature key presses within the S1-S2 interval, and extraneous baseline shifts such as those produced by body movements, were omitted in off-line averaging with a CAT 1000. Average CNVs were based on 6 to 12 trials per run, the number being constant for a given individual. CNV amplitude was measured as the difference in average voltage (sampled every 16 msec) between the 256 msec epoch pre-S2 and the 512 msec epoch pre-S1; this difference was referenced to an on-line 25-μV calibration pulse.

EKG for cardiotachometric analysis was recorded from sternum to lower left chest. Overall heart rate (beats per minute) for each condition was determined by obtaining the mean of a random sample of 20% of individual momentary heart rate in a 7-min run (20% and 100% samples yield comparable results). Eyeblinks were defined as an EOG excursion of at least 50 μV and of less than 900 msec in duration (usual duration: 150 to 300 msec). Eyeblink rate (blinks per minute) was based on the number of blinks occurring during an entire 7-min run. For the letters-recall trials, accuracy of recall (percent correct trials) was determined by dividing the number of trials in which recall of the four letters was correct by 15 (total number of trials scored). A trial was correct if letters were repeated in the same sequence given.

For comparisons among control, letters, and no-letters trials, mean differences were evaluated by correlated t-tests with 35 df (n = 36). Reported differences are significant at the .05 level or less.

Results

Preliminary evaluation of CNV amplitude, reaction time, heart rate, and eyeblink frequency for baseline and recovery control runs indicated no significant differences on each response measure. Consequently, a pooled control value (mean of the two control values) was used for statistical analysis.

Table 1 indicates means and standard deviations of CNV amplitude for pooled controls, trials with letters, and trials with no letters. For simplicity of presentation, CNV amplitude values appear in the table as algebraically positive. Differences in CNV amplitude (letters trials minus pooled controls and no-letters trials minus pooled controls) are shown in Fig. 1 for the three recording sites. Fig. 1 and Table 1 indicate that CNV amplitude is reduced in letters trials for the Pz recording site; in no-letters trials, CNV amplitude is elevated at CZ and Pz. Table 1 also indicates that CNV amplitude is lower for letters trials than

Table 1. Means (and Standard Deviations) of CNV Amplitude and Reaction Time for Three Types of Trials

Trial type	CNV amplitude, μV			Reaction time, msec
	Fz	Cz	Pz	
Letters-recall	6.14 (5.81)	11.81[a] (7.07)	5.58[a,b] (5.63)	276.03[b] (79.85)
No letters	7.28 (6.15)	14.62[a,b] (7.29)	10.38[a,b] (5.04)	260.33[b] (63.85)
Pooled control	5.84[c] (3.67)	12.19[c] (5.80)	8.31[c] (4.70)	232.86 (37.76)

[a] Letters-recall and no letters significantly different from each other.
[b] Significantly different from pooled controls.
[c] Significant differences: Cz > Pz > Fz.

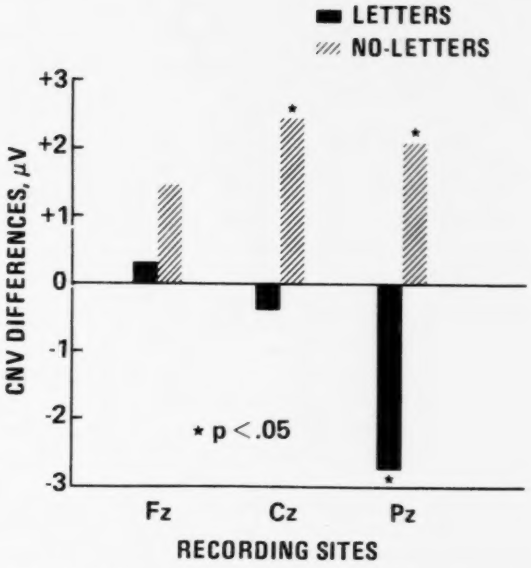

Fig. 1. CNV amplitude difference scores (letters trials minus control trials and no-letters trials minus control trials) for Fz, Cz, and Pz recording sites in a group of young normal volunteers (n = 36). The downward direction of solid bars for Cz and Pz indicates CNV reduction in letters trials compared to controls (CNV distraction effect). The upward direction of the diagonal bars at each site indicates CNV enhancement in no-letters trials compared to controls (CNV rebound effect).

no-letters trials at both Cz and Pz. Fig. 2 shows examples of CNV traces for one individual. A comparison of control values of CNV amplitude for the three recording sites shows CZ larger than Pz and Pz larger than Fz (Table 1).

Reaction times were slower in both letters and no-letters trials compared to pooled controls (Table 1). Heart rate levels were significantly elevated in the 50% letters condition ($\bar{X} = 72.99$ beats per min., SD = 10.08) compared to pooled controls ($\bar{X} = 70.19$, SD = 9.79). There was no difference in eyeblink frequency between the 50% letters ($\bar{X} = 14.08$ blinks per min, SD = 6.73) and the pooled controls ($\bar{X} = 13.14$, SD = 12.18) conditions. Mean percent of trials having correct recall of letters was 96.67 (SD = 4.65).

Discussion

Compared to control trials, the short-term memory task produced a selective reduction of CNV amplitude at Pz and a slowing of reaction time to S2 (CNV distraction effect). This finding suggests that centroposterior brain regions may mediate distraction effects involving intermittent lexical stimulation and that disruption in CNV development can be produced selectively within a block of trials. Similarly, the pattern of CNV reduction in letters trials, where two overlapping tasks were performed (listening to letters and preparing for response to tone) compared to no-letters trials, where the subject only prepared for response to tone, indicates that CNV development can be disrupted by the presence of a high information load that fractionates attentiveness to S2 (letters trials), but can be enhanced by the unexpected removal of this information (no-letters trials). That these opposite effects occurred in the same block of trials demonstrates fine-grained experimental control over one type of event-related slow potential (CNV) through the systematic alteration of information processing.

Perhaps the most important finding in this study is the unexpected elevation of CNV amplitude in the no-letters trials beyond control values, despite the fact that control and no-letters trials are physically identical; i.e., each type is made up of a flash-tone-key press. These supranormal CNV amplitudes may represent a disinhibitory effect produced by the shift from a divided attention set in letters trials (listening for letters and preparing for response to tone) to an undivided (unified) attention set in no-letters trials (simply preparing for response to tone). This interpretation is supported by subjective reports that, once it was clear early in the flash-tone interval that no

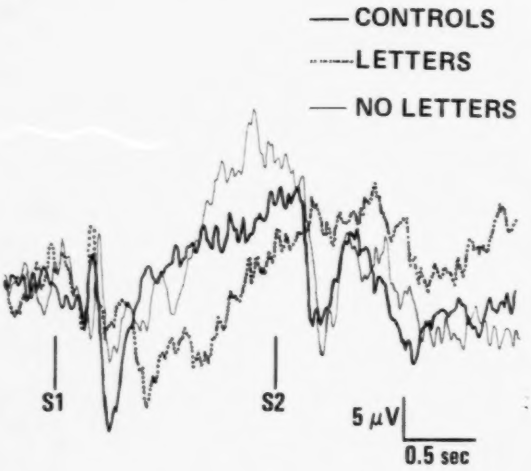

Fig. 2. Examples of CNV traces (Pz) of one individual for letters, no-letters, and control trials. Compared to the control trace, averaged CNV is reduced in letter trials (distraction effect) and is enhanced in no-letters trials (rebound effect). CNV resolution (return to baseline after S2) is incomplete for the letters ("distraction") trials, and the latency of the late positive component of the evoked response to S1 is delayed for letters trials compared to control trials. The S1-S2 (flash-tone) interval is 1.5 sec. The subject's motor response to tone is not depicted. Relative negativity at Pz referred to linked earlobes is upward.

letters would be heard, subjects quickly shifted their entire concentration to the tone task. The possibility that the CNV rebound phenomenon represents a switching of attention processes is in agreement with recent findings of diminution of this CNV effect in elderly individuals, who characteristically have difficulty in changing attention sets. Whatever the mechanism of action, the CNV rebound effect appears to be a reliable characteristic of the normal intact human brain and may provide a useful measure of plasticity in brain functioning. One group of patients with bimedial prefrontal leucotomies showed a complete absence of the CNV rebound effect (Tecce et al., this volume).

The finding of slower reaction times in no-letters trials as well as letters trials suggests that this measure may reflect a tonic distraction process in the 50% letters condition produced by the uncertainty of not knowing whether letters will be present or absent, whereas CNV amplitude reduction may reflect a more selective type of phasic distraction process intrinsic to letters trials. The fact that heart rate was elevated in the 50% letters condition suggests that this measure of cardiovascular function may be a more sensitive indicator of experimental effort and/or distraction than is oculomotor function as measured by the blink response.

Summary

Thirty-six normal men were tested in a simple reaction time task consisting of a flash-tone-key press (control trials) and in a similar task where a short-term memory task for auditory letters was either presented within the flash-tone interval or not presented (no-letters trials). CNV amplitude showed a pattern of reduction in letters trials accompanied by a slowing of reaction time (CNV distraction effect). CNV amplitude showed an unexpected pattern of elevation in no-letters trials beyond control values (CNV rebound effect). The rebound function of CNV may be a useful indicator of plasticity of functioning in the normal intact human brain.

Acknowledgments

The research assistance of Mary Beth Boehner, June Savignano-Bowman, Connie Dessonville, Debbie Meinbresse, James Kahle, and Baiba Liepins is gratefully acknowledged.

AVERAGE EVOKED POTENTIALS AND TIME PERCEPTION[1]

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Cognitive models of time perception relate time perception data to expectancy, information processing, coding and memory. Sensory physiological models of time perception, on the other hand, propose an internal time keeper or clock whose rate is influenced by general physiological activation (Rutschmann 1973, Triesman 1963, Vroon and van Boxtel, 1972).

Inferred physiological activation in time estimation has been related to independent physiological measures, particularly the EEG. Faster EEG frequency composition has been taken as an index of greater physiological activation, and thus faster clock rate, than slower EEG frequency composition. Surwillo (1968) proposed that the alpha rhythm is the visual representation of the internal clock, but data supporting this hypothesis are not definitive (Anliker 1963, Coffin 1974, Surwillo 1964, Vroon and van Bostel 1972, Woodruff 1975).

Average evoked potentials (EPs) would appear to hold considerable promise in relating time perception to both physiological and cognitive models. Certain EP components have been related to physiological activation; others have been implicated in cognitive processes involving expectancy, uncertainty, and the matching of sensory input against memory.

Recent studies illustrate how EPs might be indicative of the substrate of behavioral time estimation. In a study in which EPs and time estimation data were obtained on different trials, cortisol was found to decrease the effects of attention on the visual EP (occipital) and to increase behavioral productions of elapsed time (Kopell et al. 1970). Weinberg et al. (1974) reported emitted potentials occurring at the point in time near the end of an estimated duration. McAdam (1966) reported that the contingent negative variation (CNV) preceding keypress increased as subjects learned to produce a temporal interval. However, CNV decreased as subjects became more accurate.

Some EP studies have used methods other than production or reproduction to measure time estimation. Simernitskaya (1973) asked subjects to discriminate flashes of light according to duration when, in reality, flash duration remained constant. A negative component emerged in the parieto-occipital region at a latency of 150 msec, whereas EPs from the centrofrontal region were depressed (except for a 240-msec component recorded from the right hemisphere). Divenyi (1973) reported a relationship between overestimation of short time intervals between two tones and an increase in time between the peaks of N100 and P200. Warhonowiez (1974), on the other hand, found no rlationship between EPs and time error when subjects were required to judge the similarity or dissimilarity in duration of sound pairs.

In the following study, average evoked potentials were simultaneously recorded while subjects made judgments of a constant time interval (1 sec) between two clicks. The rationale was that differences found in EPs to the same interval could be attributed to differential time perception since the actual time interval remained constant.

Method

Eight males aged 18 to 27 years were paid for participating. Ag/AgCl electrodes were placed at Cz, Oz, and under the left eye with a left earlobe reference. EEG and EOG amplifiers were set to pass frequencies between 0.02 and 1000 Hz (half-amplitude points).

Each trial began with the onset of a fixation light that remained on throughout the trial. One second later, two clicks (1000-to 3000-Hz bandpass) separated

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by a 1-sec interval were presented. The subject's task was to judge the silent interval between the first and the second click. One second after the second click, a flash cued the subject to indicate his judgment by pressing either a left or right key with his right index finger. The intertrial interval between the flash and presentation of the fixation light for the next trial was 5.9 to 6.9 sec.

Subjects were instructed that the task would involve a difficult discrimination of two different silent time intervals bounded by clicks. Before each block of 20 trials, they were given an example of the short interval (e.g., 990 msec) and of the long interval (e.g., 1010 msec), ostensibly for reference and practice. During experimental trials, however, only a 1000-msec interval between clicks were presented, although subjects were told that approximately 50% of the intervals would be short and 50% of the intervals would be long. A random program was used to determine the subject's "accuracy" and payoff (a dime added for each "correct" discrimination, or subtracted for each "incorrect" discrimination), and subjects were informed at the end of each block how much they had won or lost in that block. There were 400 trials, 20 blocks of 20 trials each, and some subjects were retested on a second day.

In addition, one subject was run on a variation of the above design. Experimental blocks were composed of a random sequence of trials with either a 990- or 1010-msec interval between clicks. EPs were averaged separately for short and long intervals, and for correct and incorrect discriminations. Approximately 1 to 3 sec following the subject's response, a feedback click was delivered following a correct discrimination only (first session) or following an incorrect discrimination only (second session).

Trials with eye movement were discarded. Components were measured from peak-to-peak and from baseline-to-peak with baseline determined by visual estimation of voltage over a 100-msec period before presentation of either the first or second click. In addition, the CNV was measured as the most negative point within the 1000-msec interclick interval relative to the baseline preceding the first click. Differences were assessed by t-tests for correlated data.

Results

The N94, P187, and N274 vertex components were consistent across subjects and were systematically measured, however, occipital records were not measured because of inconsistencies across subjects and alpha contamination in two subjects. For some subjects, a late occipital positive component following the second click could be identified (P300?), particularly for judgments that duration was short.

No significant differences between vertex EPs associated with judgments of short versus judgments of long were found for the first click or for the height of the CNV.

Vertex EPs for the second click averaged separately for trials judged short and for trials judged long are shown in Fig. 1 for all eight subjects. None of the measurements of N94, P187, or N274 from baseline was significantly different between conditions. However, the peak-to-peak measure of P187-N274 was larger for long judgments (5.5 μV), than for short judgments (3.7 μV) measurements indicated that the difference was largely due to variation in the N274 component.

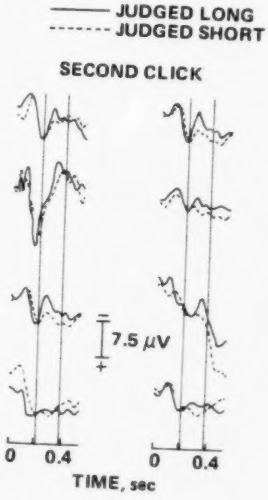

Fig. 1. Vertex auditory EPs ($N \approx 200$) elicited by the second click delimiting the end of the estimation interval for eight subjects. Responses associated with intervals judged short and intervals judged long are aligned on P200. Vertical lines delimit the latency window within which area difference measures were made.

EPs of long and short trials differed in the latency range between 213 and 387 msec following the presentation of the second click. This region is bounded by the two vertical lines in Fig. 1. Since the difference appeared consistently within a given EP latency region, the following measurement was devised: EPs for long and for short judgments were aligned on P187 (as in Fig. 1), and the area of the difference in the 213-to 387-msec region was measured with respect to whether the waveform was more negative or positive for long than short judgments. Results indicated that the waveform was more negative for long than short judgments within this time window ($p < .01$).

Fig.2 shows data obtained from the single subject run on the random sequence of short and long

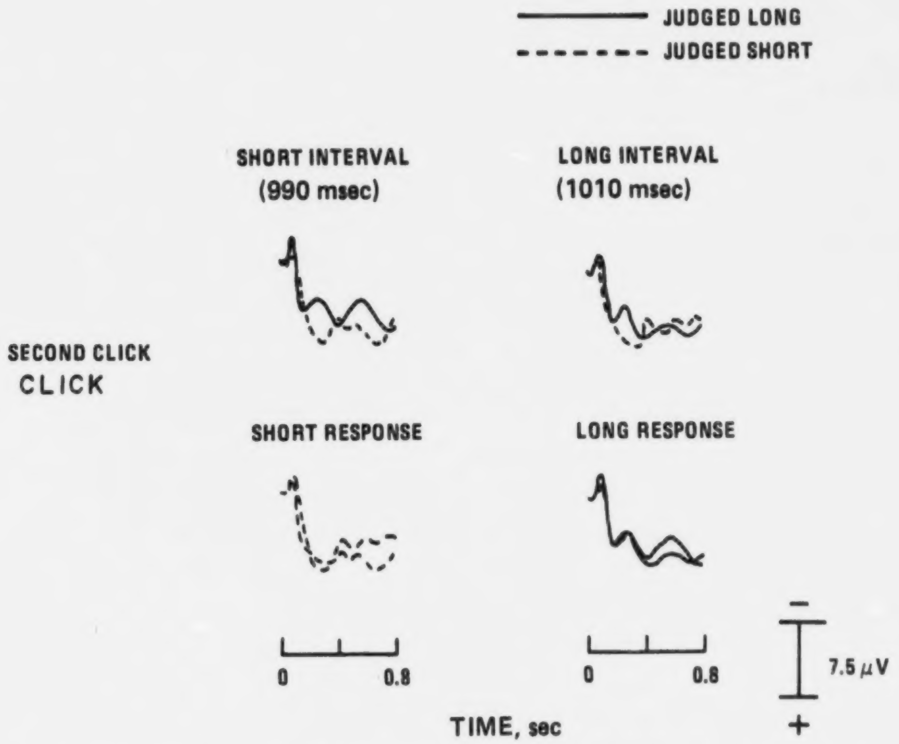

Fig. 2. Vertex auditory EPs (N ≈ 100) elicited by the second click delimiting the end of the estimation interval for one subject. Waveforms at the top (overlapped at baseline) show differences associated with short and long judgments for the 990-msec and 1010-msec intervals separately. The same waveforms are overlapped at the bottom to indicate that the waveshapes are similar for the same response category regardless of whether the actual interval was 990 or 1010 msec.

intervals. Again, the waveforms for intervals judged long is more negative in the N250 region whether or not the interval was actually short or long. (The subject judged 53% of the trials correctly). EPs obtained for the feedback clicks showed a larger early P300 that was larger for feedback indicating an incorrect than correct judgment.

The behavioral data were inspected for evidence of a "lengthening" of the perceived interval over time (indicative of a slowing down of clock rate with time). "Lengthening" in this case would be indicated by an increasing proportion of short judgments. No consistent increase in the proportion of short judgments either across blocks or within blocks of 20 trials was found. (Four subjects showed lengthening across blocks, one showed shortening, two showed no change and one subject's behavioral data were not recorded.) However, subjects produced more short ($\bar{x} = 66\%$) than long ($\bar{x} = 34\%$) judgments during the experiment ($p < .02$).

Discussion

Auditory EP differences related to perception of elapsed time were found. Differences between long and short judgments were apparently subjective and unrelated to actual elapsed time, which was constant or was varied by such a small amount that chance performance resulted. This aspect of the design is similar to that of Begleiter and Porjesz (1975). In their study, visual EPs to the same medium-intensity flash differed depending upon whether the flash was judged as dim or bright.

Although it is important to demonstrate that average EPs reflect subjective time judgments, the differences can be interpreted further. A relationship between increased amplitude of the N250 component and lowered arousal has been suggested (Wilkinson et al. 1966), and the P300 EP component has been related to variables of a more cognitive nature (see Tueting, this volume). The P300 component may be partially overlapped in time with the N250 component at vertex under certain experimental conditions (Friedman et al. 1973, Prichep et al. 1976, Tueting 1968; Tueting, this volume). In fact, it is known that several components can occur in this latency region, and it is not always possible to delineate them.

EP differences to the second click appear to be opposite to differences expected on the basis of clock theory. In terms of a physiological model of time perception, judgments that the interval was long should be associated with a faster clock rate and thus greater physiological activation (smaller N250). Instead, the results indicated that long judgments were associated with a larger N250 component. In addition, no EP differences were found to the first click that initiated the beginning of the estimation interval. Presumably, differences in a tonic state of physiological activation, if present, would have affected the click initiating the estimation period as well as the click ending the estimation period.

The findings appear to relate better to a cognitive model than to a physiological model of time perception. As mentioned above, a larger positive component associated with cognition may overlap N250 in vertex recordings. The presence of a P300 component for short judgments can be seen in Fig. 2, and the component was also seen in occipital recordings for some subjects.

There is no direct evidence from this study concerning what cognitive aspects may have resulted in larger P300 for judgments of "short." P300 amplitude has been related to lower response probability (Karlin and Martz 1975), but in the present study 66% of the judgments were "short"–the category with larger positivity in the P300 region. Information from other studies indicates that larger P300 components are associated with stimuli possessing greater salience (Jenness 1972) and greater decision confidence (Squires et al. 1975). It is not immediately obvious which of these aspects might have been involved. Greater salience for short is suggested by the larger percentage of short judgements, However, greater decision confidence for short judgements is also a viable explanation because the accuracy of time judgment (in absolute units) generally decreases the longer the intervals to be judged, and greater temporal uncertainty is related to smaller P300 amplitude (McCarthy and Donchin 1975).

In order to assess alternative explanations proposed for the data in terms of P300, more systematic study is obviously required. A direction for further study would propose the use of a wider range of time intervals to be judged and a wider range of verbal estimates by the subject. The relationship of EPs to time perception accuracy could then be more precisely studied, perhaps within a signal detection framework. Since the P300 component can be isolated from N250 by the modality-specific distribution of N250, information on topographical distribution would be desirable. In any case, the findings of the present study suggest that investigation of EP correlates of the judgment of elapsed time may reveal previously unavailable information concerning the state of the subject during a behavioral time estimation task.

Summary

Average evoked potentials associated with short versus long judgments of elapsed time were recorded. On each trial, two clicks separated by a silent interval to be estimated were presented. This interval was always 1 sec in duration. EP amplitude to the second click delimiting the end of the estimation interval was more negative in the N250 region (213 to 387 msec) for judgments that the interval was long than short. No differences were found for EPs elicited by the first click or for the CNV. These findings indicate that average EP differences can reflect time judgments that are entirely subjective. Further, the results do not seem to correspond to a sensory physiological model relating activation to the rate of a hypothetical internal clock. A cognitive explanation involving the P300 component (which may be partially overlapped in time with N250) was considered likely, e.g., greater salience or more decision confidence for "short" judgments.

ATTENTION AT THE COCKTAIL PARTY: BRAINSTEM EVOKED RESPONSES REVEAL NO PERIPHERAL GATING

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When a subject is presented simultaneously with two different spoken messages, one fed into each ear, he is usually able to focus his attention effectively on one message to the exclusion of the other (Cherry 1953). In fact, when instructed to attend to a normal speech passage in one ear, subjects typically can recall only rudimentary information about the passage in the unattended channel (such as the sex of the speaker), as if somehow that message had been "shut out" before processing was complete. The problem of how one can attend to one channel of auditory input to the exclusion of other competing channels has come to be known as the "cocktail party problem," since similar mechanisms are presumably involved in following a conversation in a noisy room. The subjective experience of shutting out, or gating, the irrelevant inputs has found theoretical expression in theories of attention that propose a filtering (Broadbent 1958) or attenuation (Treisman 1964) of unattended inputs.

In its most radical physiological form, the gating hypothesis suggests that sensory inputs are attenuated near the auditory periphery through descending efferent inhibitory systems. Several years after Cherry's demonstrations of dichotic attention, Hernandez-Peon (1956) claimed to find support for such a radical position; click-evoked responses in cats were reduced in amplitude at the cochlear nucleus when the cat was distracted by visual or olfactory stimuli. Subsequently, however, this influential experiment was criticized on methodological grounds: head and pinna movements of the cats could have reduced effective stimulus intensity and diminished cochlear nucleus evoked responses regardless of efferent attenuation (Worden 1966). When care was taken to stabilize acoustic input, evoked responses at the cochlear nucleus were found to remain stable despite attentional manipulations (Wickelgren 1968).

In several recent experiments that maintained careful control of the acoustic input, however, modifications in brainstem evoked activity were reported with changes in behavioral state (Oatman 1971, Suga and Shimozawa 1974). Similarly, changes have been reported in auditory evoked unit responses in the cochlear nuculeus (Buchwald and Humphrey 1972), Olesen et al. 1975), medial geniculate (Gabriel 1975), and brainstem reticular formation (Olds et al. 1972) as a function of habituation or conditioning procedures. These studies reaffirm the possibility that efferent modulation of input plays a role in some forms of auditory attention.

Techniques have recently become available for measuring click-evoked, far-field electrical activity generated in the human brainstem (Jewett and Williston 1971). Such brainstem evoked responses (BERs) permit a reexamination of the peripheral gating hypothesis in paradigms known to produce powerful selective-attention effects in man. In the first such study, Picton and Hillyard (1974) examined auditory (evoked potentials during click intensity discrimination and in a control condition when clicks were ignored. They found no significant change in any brainstem evoked component, but substantial enhancements in the late waves (N1-P2) when attention was focussed on the train of clicks. Similar effects of attention upon the late cortical evoked potentials have been reported in a variety of selective-attention paradigms where the subject was required to focus attention on one channel to the exclusion of others (see Hillyard and Picton 1978 for a review). In a recent study, Hink and Hillyard (1976) found late wave correlates of selective attention to dichotic speech passages. Both N1 (80 to 120 msec) and P2 (160 to 200 msec) components were enhanced to neutral vowel probe stimuli when attention was directed to a superimposed prose passage in that ear.

In the present study, the dichotic speech paradigm was used to investigate possible attention-related modifications of probe-evoked BERs. Some evidence suggests that the efferent auditory projections, which are anatomically well-established in primates, might be functionally engaged by such ecologically appropriate and acoustically complex stimuli. For example, Dewson (1968) reported that macaques were impaired in their ability to make difficult phoneme discriminations presented in masking noise following section of the efferent olivo-cochlear bundle. Presumably, such efferent modulation, if it also exists in man in comparable situations, should be reflected in attention-related changes in the BER.

Methods

Six paid student volunteers served as subjects. They reclined in a dimly lit, sound-treated chamber and listened through headphones while different prose passages were presented independently in each ear. A female voice read from a novel in one ear, while a male read a separate story in the other; superimposed on each passage were bursts of click stimuli delivered independently in the two ears. Click triggers and spoken prose passages were recorded on a four-channel audio tape system in such a way that during active conditions, the click probes and the speech itself always occurred concurrently in a given ear; i.e., clicks never occurred without speech in the same channel. During control conditions, speech inputs were disconnected and clicks were presented in isolation.

Click stimuli were 100-μsec pulses of gated white noise, presented with ISIs of 40 msec, in bursts of six. The minimum interburst interval was 100 msec. Click intensities in each ear were adjusted to 61 dB sound pressure level (SPL) and maximum speech intensities for both male and female voices were set at 60 dB SPL. Subjects attended to one channel of prose or the other in a counterbalanced design, and answered a short questionnaire on its contents after each 5 to 10-minute segment. Male and female voices were also counterbalanced across ear of delivery.

BERs were recorded from vertex-right mastoid and left mastoid-right mastoid configurations, amplified (bandpass set at 10 to 3000 Hz), and stored along with appropriate trigger pulses on audio tape (bandpass 30 to 16,000 Hz) for subsequent off-line averaging. Mid-latency and late evoked potentials were recorded from Cz, T3, and T4 derivations and from the upper orbit, each referenced to the right mastoid process. They were amplified (bandpass set at 0.15 to 500 Hz) and stored on an FM tape recorder (bandpass 0 to 150 Hz) for subsequent off-line analysis on a signal averager. All inter-electrode impedances were maintained below 4 KΩ. Each experiment lasted 2 hours, with BERs recorded to approximately 120,000 probe stimuli.

Results

Subjects attended effectively to the relevant channel and reported typical cocktail party effects; i.e., the unattended messsage faded away, was shut out, or was blocked from awareness. Despite this powerful subjective impression of input filtering, none of the BER components changed significantly in either latency or amplitude as a function of attention.

In vertex-to-mastoid derivations, six positive-going components (waves I-VI of Jewett) and the prominent negative deflections after waves I (Labelled I′), III (III′), and VI (VI′) were identified in all subjects (Fig. 1 shows representative tracings from two subjects). Mastoid-to-mastoid records showed prominent early waves, particularly wave III, with much attenuated late components (IV–VI); again, there were no significant attention-related changes in amplitude or latency of any component.

Tables 1 and 2 show the stability of amplitudes and latencies of different components of the vertex-to-mastoid BER as a function of attention: analysis of variance (subjects x ear x sex of speaker x direction of attention) did not reveal any significant attention-related changes in amplitude or latency of any component. The large number of click-evoked responses (96,000 per subject) provided high signal/noise ratios and low variances for each component, as shown in Table 2. For example, the 95% confidence interval established around the peak-to-peak V-VI′ measure showed that any attention-related changes would be less than ±5.27% of the overall mean amplitudes.

In most subjects, midlatency (10 to 30 msec) responses were also recorded; they were highly variable in amplitude both within and between subjects and were not systematically related to attentional manipulations. This variability is presumably due to the large myogenic components in this latency range (Picton et al. 1974b). The N1 and P2 components elicited by each burst were too small to be reliably quantified, consistent with the well-established refractoriness of these vertex potentials, both with repetitive monaural stimuli (Davis et al. 1972) and between the ears (Butler 1972).

Discussion

The stability of the BER suggests that peripheral gating of the rejected input does not occur when attention is focused on one channel of dichotic speech. Such observations are consistent with theories of attention that suggest that all sensory inputs are fully analyzed in parallel regardless of attentional focus (Deutsch and Deutsch 1963, Norman 1968). This result is also in accord with the Broadbent/Treisman models of attention, which claim that selection between stimulus channels can occur on the basis of simple cues, such as spatial position or frequency, provided such selection occurs beyond the brainstem

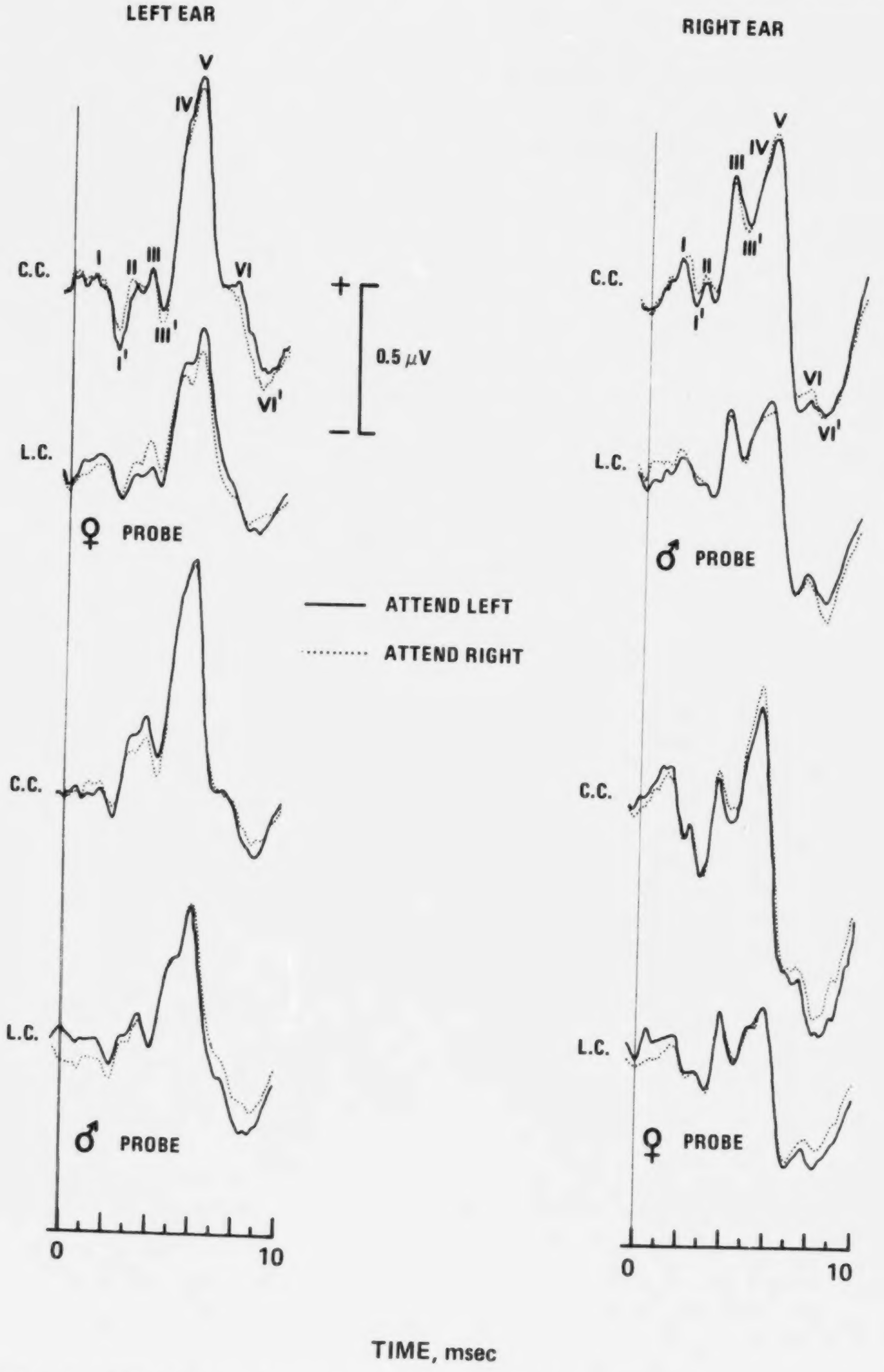

Fig. 1. Click-evoked BERs from two subjects (sisters C.C. and L.C.) during attention to left and right ear messages. Click probes were superimposed on female and male voices in left and right ears, respectively, in the top pairs of tracings; voices were reversed in lower tracings. N = 12,000 responses/average.

Table 1. Mean Latency and Baseline-Peak Amplitude of Each Component in the Brainstem EP to Attended and Nonattended Clicks

	Component						
	I	II	III	IV	V	VI	VII
Latency, msec							
Attended	1.58	2.71	3.67	5.11	5.86	7.31	8.38
Nonattended	1.56	2.80	3.65	5.08	5.77	7.34	8.34
Standard deviation	± 0.036	± 0.065	± 0.015	± 0.024	± 0.050	± 0.020	± 0.033
Amplitudes, μV							
Attended	0.08	-0.03	0.11	0.25	0.39	-0.22	-0.42
Nonattended	0.06	0.01	0.15	0.26	0.41	-0.21	-0.39
Standard deviation	± 0.009	± 0.033	± 0.030	± 0.024	± 0.019	± 0.025	± 0.027

Table 2. Mean Peak-Peak Amplitudes (μV) of Brainstem EP Components and the Percent Difference in Amplitude (±se) between Attended and Nonattended Conditions

	Components					
	I-I′	I′-III	III-III′	III′-V	V-V′	V-VI′
Attended	0.213	0.244	0.165	0.444	0.600	0.808
Nonattended	0.193	0.257	0.167	0.455	0.601	0.808
Standard deviation	± 0.016	± 0.012	± 0.016	± 0.022	± 0.016	± 0.015
Difference	+9.8	-5.18	-1.20	-2.45	-0.17	0.00
Standard error	± 7.8	± 5.9	± 8.9	± 4.7	± 2.7	± 2.3

level. In fact, it has been suggested that such a telencephalic selective mechanism is reflected in attention-related changes of the auditory-evoked N1 wave (Hillyard and Picton 1978).

While the present study seems to rule out a crude attenuation of all input to the unattended ear, the possiblity of fine-tuned peripheral attention cannot be excluded. Recent work by Hecox (1974) established that the BER is generated almost exclusively by high-frequency-sensitive portions of the cochlea and auditory pathways. Since the frequencies that contain most of the linguistic information in human speech are below those that contribute to the BER, attenuation restricted to speech frequencies might still occur in unattended channels with little accompanying change in the BER itself.

These results are concordant with studies demonstrating the stimulus-bound character of the BER (Picton et al. 1974, Hecox and Galambos 1974), and the stability of the BER during changes in arousal or attention (Amadeo and Shagass 1973, Picton and Hillyard 1974, Jewett and Williston 1971).

The absence of any attention-related change at N1 latencies in this study is somewhat surprising, since such effects have been shown to occur in similar experiments where the probes more closely approximated the acoustic properties of the speakers' voices (Hink and Hillyard 1976). Perhaps the evocation of N1 is more finely tuned during attention to normal speech than it is in less natural tasks, so that high-frequency probes were excluded from the attended channel by spectral considerations alone, regardless of the ear of presentation. A second possibility is that the attention-related increases in 80-to-120 msec negativity of N1 (Schwent and Hillyard 1975) do not occur when ISIs are so short as to eliminate the N1 altogether.

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IV. LANGUAGE

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LANGUAGE AND EVOKED POTENTIALS[1]

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Introduction

Although the study of language and evoked potentials (EPs) is relatively young, with few published studies, the field appears to be gaining momentum and sophistication. This area is particularly difficult to evaluate since nearly all the problems of other areas of EP research must be considered, along with the linguistic ones. Distinguishing language effects *per se* from both lower-order effects, such as sensory, motor, and artifactual, and higher-order effects, such as general states and cognitive processes, is difficult. Thus, key issues often revolve around the question of the specificity of EP differences that might be related to language.

In the preconference correspondence among the panel members (listed later), some 21 issues associated with relating language functions to evoked potentials were identified. Discussion in this section has been organized around six topics, each of which is treated in a short essay following this brief overview. The topics are (1) Issues in Neurolinguistics: Evoked Potential Analysis of Cognition and Language, (2) Distinguishing Linguistic and Stimulus Effects, (3) Lateral Asymmetry of Evoked Potentials and Linguistic Processing, (4) Individual Differences and Similarities in Language Effects on EPs, (5) Contributions of Linguistics and Other Data Bases, and (6) Methods of EP Analysis in Linguistic Research.

Following these essays, three papers on specific research related to language and evoked potentials are presented: (1) a study of semantic versus lower order effects of linguistic stimuli by A.L. Megela and T.J. Teyler, (2) a study of response to language stimuli in children with reading disabilities by S.A. Shelburne, and (3) a study of the effect of electrode placement and recording montage on CNV amplitude preceding speech by S.H. Curry, J.F. Peters, and H. Weinberg.

Panel members and mini-reviews of their research

Members of the panel on language and evoked potentials were:

1. W.S. Brown, University of California, Los Angeles, California.
2. R.M. Chapman (chairman), University of Rochester, Rochester, New York.
3. D. Friedman, New York State Psychiatric Institute, New York, New York.
4. D. Molfese, Southern Illinois University, Carbondale, Illinois.
5. S.A. Shelburne, Jr., University of Cincinnati, Cincinnati, Ohio.
6. T.J. Teyler, Harvard University, Cambridge, Massachusetts.
7. R.W. Thatcher, New York University School of Medicine, New York, New York.

At the beginning of the language session, each panelist briefly reviewed his research to provide a common basis for discussion and to focus attention on specific issues.[2] Mini-reviews are useful here also, since the essays focus on the same issues and refer to relevant aspects of research only as examples.

Shelburne has been studying reading disabilities with the aim of developing diagnostic neurophysiological techniques. He visually presents letter stimuli to subjects whose task is to indicate whether the stimuli make a word or nonsense syllable. The stimuli are formed of three letters presented at 1-sec intervals: blank, letter, letter, letter, blank. For each word there is a matching nonsense syllable that has the same first two letters. Thus, the subjects cannot distinguish between word and nonsense syllables until the third stimulus is flashed.

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[1] Supported in part by the National Institutes of Health Research Grant 5 RO1 EY01593 to Robert M. Chapman.

[2] A transcript of discussion that took place at the meeting has been prepared and is available from the Chairman at cost.

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Each trial run included a randomized presentation of 50 words and 50 matched nonsense syllables. When subjects achieved a score of 95 percent or more, a clearcut difference emerged between EPs to the third letter and EPs to the first or second letter and a marked difference was evident between third and first position responses. The latter was probably a P300 effect, perhaps related to resolution of uncertainty. Children with reading disabilities scored near chance level of 50 percent and did not show the third position–first position EP effect. Normal children too young to read did not exhibit the EP effect. Children with reading disabilities have the following profile: (1) poor task performance in older child (9 to 12 years), (2) no visual EP difference between the final and first two stimuli within a trial, and (3) low level of eye movements (EOG). Normal children show considerable eye movement during this task.

Molfese has been especially concerned with EP aspects related to acoustic and speech sounds. Speech is composed of acoustic stimuli organized with particular characteristics. Molfese has studied parts of the brain response that reflect changes in a consonant-vowel syllable versus a vowel syllable, with non-speech controls of narrow bandwidth that do not sound like speech. He has investigated a variety of subjects along the developmental continuum. The data from neonates (only a few days of age) are particularly important. Using principal components analysis, EP components related to these speech stimuli differences were identified. For example, one component seems to differentiate between steady-state stimuli and stimuli with transitions. Another component appears to be related to the bandwidth of the auditory stimuli.

Brown has studied EP correlates of contextual meaning of words using auditory presentation. He employs homophone stimuli, i.e., words that sound alike but have different meanings depending on context. Brown presents these words in a phrase or sentence context that gives them specific meaning and then separately averages the EPs to the same sounding word in different contextual meaning phrases. For example, "rose" is studied in such phrases as: "a pretty rose," "chairs in rows," "his temperature rose," and "a boatman rows." For each electrode locus, he compares the EP waveforms derived from the four meanings. Brown has used three statistical methods: (1) coefficient of correlation between EP waveforms, (2) discrimination index based on correlation coefficients, and (3) stepwise discriminant function analyses. He consistently found that over the left hemisphere, particularly from the left anterior electrode close to Broca's area, different average EP waveforms were associated with different word meanings. Over the right hemisphere the EP waveforms for different word meanings were more similar. In these experiments, the subjects do not speak; therefore, this technique is not comparable to phonation. The EP differences were related to whether the stimuli were ambiguous in meaning, which was manipulated by order of phrase presentation and instructions to the subject.

Teyler has explored semantic meaning effects using verb/noun homophones. In one phase, subjects were instructed to think of the word when a click probe was presented approximately a second after the subject heard the word. Waveshapes of EPs were distinctly different for verb and noun meanings associated with physically identical stimuli, but were quite similar over both hemispheres for a given word meaning. Different subjects appeared to have relatively unique EP waveforms for a given word, and these were relatively stable across experimental conditions. A positive peak at about 180 msec tended to have a shorter latency for the verb meaning. Subsequently, Teyler explored an habituation/generalization paradigm in which a word was repeated seven times and then either the same or a different stimulus word was presented. Later parts of the EP, predominantly P300, were very sensitive to the generalization task. For semantically similar stimuli, e.g., synonyms like "couch" and "sofa," EPs from the Wernicke's area derivation did not dishabituate. By contrast, EP dishabituation was found when the stimulus word was changed to semantically different words that were physically rather similar, e.g., "cut" and "cup." Frontal derivations were insensitive to manipulation of linguistic stimuli.

Thatcher employed a delayed semantic matching paradigm using synonyms, antonyms, and neutral words presented visually. The control stimuli were random dot patterns. For example, a trial might contain control stimuli and the words "small" and "little." The subject's task was to indicate the semantic category of the second word in relation to the first. The second word is a synonym a third of the time, an antonym a third of the time, and neutral a third of the time. This experiment is designed to extend the match-mismatch paradigm beyond stimulus features to a semantic level. EP asymmetries were found to second words, particularly in the 400- to 500-msec range (P400). EP asymmetries to the random dot stimuli were not obtained. Significant differences in P400 amplitude were found between antonyms and neutrals, between synonyms and neutrals, and between second and first words. The effects were maximal in posterior rather than anterior regions.

Friedman reported work with two kinds of paradigms using word stimuli, a vigilance paradigm and sentences with one word incomplete. In the vigilance paradigm, the subject was asked to detect a designated target stimulus among a group of auditory stimuli. The stimuli were words, e.g., "pint," "bowl," and "kick," and human-generated, nonlanguage sounds, e.g., whistle, cough, and "psst." Another condition was a nontask in which the subject listened passively. P300 amplitudes from smallest to largest were obtained for no-task stimuli, nontarget stimuli, and target stimuli. This occurred equally for words and human-generated sounds. Although this paradigm used words, it did not require engagement of linguistic processes, since the task could be successfully performed on the basis of acoustic characteristics.

Friedman and coworkers then used a paradigm in which subjects had to use meaning in order to complete the task. Sentences in which the first grapheme of one word was missing were presented visually. The basic sentences were: "The heel is on the shoe." "The peel is on the orange." and "The wheel is on the axle." In one condition, the first grapheme of the second word was omitted, and so the subject saw "eel" in all cases. Following the last word of the sentence, the subject indicated what the second word was on the basis of the context provided by the last word. In the second condition, the second word was presented in full so that the last word provided no further task-relevant information. Whenever a word delivered information, i.e., last word in the first condition and the second word in the second condition, the peak latency of P300 was longer. Another finding was that P300 was always largest for the last word in the sentence regardless of whether it delivered critical information. This effect was called "syntactic closure."

Chapman has studied EP effects related to a particular area of semantic meaning, i.e., Osgood's (1964) analysis of connotative semantic meaning. From Osgood's analyses, specification of connotative meaning of words has emerged on three orthogonal dimensions: evaluative, potency, and activity (E, P, and A). Words that belong to six semantic classes (E+, E-, P+, P-, A+, A-) were selected as the extremes on these semantic dimensions. For example, three words that belong to the E+ class are "fresh," "pleasant," and "quality." At the opposite end of the evaluative dimension, examples of the E- class are "enemy," "tragedy," and "devil." For an experimental list, 20 words in each of these six parts of connotative semantic space were selected. On each trial, the sequence was a fixation stimulus, followed 0.5 sec later by a stimulus word. The task at the simplest level was to repeat the word late in the 2.5-sec interval following the presentation of each word. Stimulus words were randomly intermixed so that neither semantic class nor particular word could be anticipated. EPs were averaged across the 20 words in each semantic class.

Multivariate analyses revealed reliable EP effects related to semantic classes. These EP analyses were based on standardizing the data within each subject's data set, computing a principal components analysis on the entire set of data, and using the component scores as the EP measures entering the multiple discriminant analyses. The effects were consistent enough to classify EPs belonging to the various semantic classes by discriminant analyses, which used the same classification functions for all subjects. When classifications to opposite ends of one semantic dimension at a time were made, the overall success rate was 97%. The jackknifed cross-validation, which leaves each EP out of the development set and then classifies it, has an overall success rate of 90%. Two lists of words were used so that the generality of the EP effects could also be assessed by applying classification functions based on data from one word list to data obtained with the other word list. The overall other-list cross-validation success rate was 73%. Additional multiple discriminant analyses were computed to classify EPs into all six semantic classes at once, in which case chance is 16.7%. For these multidimensional analyses, the overall success rate was 55%, jackknifed cross-validation was 42%, and other-list cross-validation was 40%. These success rates were more than twice chance level.

Concluding remarks

Because there is no universal agreement on the definition of linguistics or linguistic theory, seeking EP relationships may appear to be a severe problem. The status, however, is similar to that of other fields, such as learning, for which agreement on definition and theory is lacking. Nevertheless, many instances of learning are agreed upon, and detailed effects of learning variables have been studied. Psycholinguistics is a relatively young field, but research has been sufficient to promote a body of linguistic data that could form the basis of related EP research. It is not necessary to wait for linguistics to get its house in order before embarking on EP research; in fact, the results of EP research may help delineate and constrain linguistic theory. Many on the panel believe that applying some aspects of these linguistic data would be helpful in EP research rather than simply using common-sense notions of linguistics.

Two major categories of language processing are production and reception. Both categories present a similar problem of distinguishing language processing from the more peripheral effects of motor and sensory processes. If language production were invariantly linked with particular motor processes and language reception with particular sensory processes, language-specific effects in EPs would be very difficult to distinguish. At some levels of linguistic analysis there is evidence that such linkages are not invariant. Thus, disassociation of linguistic effects from sensory and motor effects may be possible in EP research. Many linguistic distinctions have alternative representations with which to vary sensory/motor variables independently of linguistic variables.

One of the strongest supports from non-EP research for differentiating language-specific effects in EPs comes from findings of cerebral localization in linguistic studies of brain damage and dichotic studies in normals. As the result of this type of research, emphasis has been placed on lateralization and localization in EP-language research. This heavy emphasis on place may have detracted from interest in studying functional relationships between EPs and linguistic variables themselves.

Linguistic variables that might be studied include phonemes, graphemes, morphemes, syllables, words, phrases, syntax, and semantics. Beginnings have been made in many areas. In some studies a linguistic and nonlinguistic variable are compared, and in others variations of linguistic variables themselves are investigated. To recommend a single type of experimental strategy or linguistic variable would be premature. Rather, the recommendation is to design studies that are based on information available in linguistics, psycholinguistics, and psychology with careful consideration of various kinds of controls. These include consideration of sensory and motor controls, as well as general cognitive and state controls.

EP effects have been related to various aspects of linguistics. Research varies considerably in sophistication and how convincingly the EP effects may be uniquely tied to the linguistic variables being manipulated. In many cases, alternative explanations may be found in terms of sensory differences in stimuli, different states of the subject, or different cognitive functioning. This is a common situation in science; evidence supports hypotheses while alternative hypotheses may account for the same data. A great deal of careful research may be needed to assure that a particular effect is reasonably interpreted as a linguistic effect rather than the result of other variables. Amassing data of essentially the same type can be used to assess the reliability of particular EP effects, but it is of little use in assessing the validity of the interpretation.

In order to ascribe an EP effect to a linguistic variable, different strategies are needed. One strategy is to systematically relate EP effects to an established conceptual framework, i.e., intralinguistic variation within the framework provided by one of the well-tilled subfields in linguistics. This strategy suggests a systematic approach to EP measurement in which specific parts of the EP can be identified, measured, and related to linguistic variation. The more detailed the meshing of EP data with linguistic data is, the more convincing the linguistic interpretation.

Another related strategy is based on converging lines of evidence. If a particular linguistic variable is known to affect communication or behavioral performance in predictable ways in several different situations, one can study the generality of related EP effects in these different situations. One example would be to find an EP effect in normal adults that appears to be related to function words such as articles and prepositions. This EP effect could then be tested in patients with Broca's aphasia, a feature of which is the omission of these function words. A further line of evidence could be sought in children's data, since these function words are omitted during certain stages in language acquisition. An interesting aspect of this example is that the developmental order of appearance of these words in a vocabulary is different from the difficulty ordering in Broca's aphasia adults.

A third strategy to foster convincing linguistic interpretations of particular EP effects is to use systematic control procedures. One could design experiments to hold linguistic effects constant while varying the confounded variable. If EP changes are observed in this design, the question is whether the part of the EP that changes is different from the part ascribed to the linguistic variable. For example, the same semantic meaning may be carried by different words so that the confounded variable of different physical stimuli could be varied to test for the specificity of particular semantic meaning effects. The converse procedure of holding the confounded variable constant while varying the linguistic variable is also possible. For example, some physically identical words have quite distinct semantic meanings as in the research on homophones. Another example, illustrating a different kind of confounded variable, is to hold the subject's task constant, e.g., a match-mismatch task, while varying the linguistic elements of paired presentations.

The specificity of language effects depends in part on the dimensionality of EP measures. For example, if only a single measure, say amplitude of apparent P300, were extracted from EPs, then demonstrating specificity may be hopeless. Let us pretend that nouns and verbs elicit different amplitude P300s. One might argue that this is not a specific language effect because P300 amplitude is also modulated by other variables, such as stimulus uncertainty. This situation would be very similar to finding a difference in pupil dilation to nouns and verbs; one would hardly argue that the pupil was directly involved (a necessary link in the causal chain) in the linguistic processing of nouns and verbs. One might still find it useful, however, to utilize the pupil measure (or P300 measure) in studying linguistic processing since a reasonable interpretation is that the linguistic processes *per se* systematically influence these general processes. If there were particular parts of EPs that related more specifically to noun-verb processing, they would not be found by simply measuring P300 amplitude in the manifest waveform. It would be necessary to use EP measures that focus on purely linguistic parts of EPs. Possible solutions include: (1) to use the difference between EPs with and without the particular linguistic processing and (2) to use multivariate statistical analyses, which potentially take into account all of the time points within EPs as well as their relationships. To separate a noun-verb part from a stimulus-uncertainty part of the EP, at least two measures of the EP that respond differently to these two kinds of variables must be made. These measures must vary independently or at least be manipulated to different degrees. Thus, the dimensionality of the interpretations of specificity are limited to the dimensionality of the EP measures and the dimensionality of the experimental design.

ISSUES IN NEUROLINGUISTICS: EVOKED-POTENTIAL ANALYSIS OF COGNITION AND LANGUAGE

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Introduction

Currently, there is controversy and confusion about the presence or absence, as well as the exact nature of the distinctions between cognition and language. Some authors argue that there are no distinctions (Menyuk 1975); others argue that cognition is dependent on language development (Blank 1975). Still others consider language secondary to the development of cognition (Furth 1975). Much of the present controversy is due to differing definitions of cognition and language. No clear agreement on exactly what the word "cognition" means has been decided upon. This lack of agreement seems to be due, in part, to the fact that different investigators have different perspectives. For instance, developmental psychologists generally define cognition in terms of the development from birth to adulthood of skills such as assimilation, object permanence, conservation, and development of logical operations (Piaget 1971a, Langer 1974). Speech pathologists and linguists tend to define cognition in terms of specific mental abilities with less emphasis on age dependence, such as adult thought patterns, symbolic representations, and mathematical function (Rieber 1975). On the other hand, cognitive psychologists tend to use a broader definition such as that offered by Neisser (1967) as "processes by which sensory input is transformed, reduced, elaborated, stored, recovered, and used." Finally, neurophysiologists have yet to enter into this area in a meaningful way and thus have not attempted to formulate a clear definition.

This section of the EPIC IV Conference is concerned with evoked-potential correlates of language and cognition; however, the field of neurolinguistics, which is in its infancy, has not adequately come to grips with the problem of defining cognition. For want of a better procedure, therefore, the broader definition used by cognitive psychologists will be adopted for purposes of the present discussion. This strategy is justified on the basis that sensory, memory, and motor transformations hold a fundamental position in all of the current definitions of cognition and yet do not preclude elaborations performed on these elementary functions. Furthermore, emphasis such as Neisser's (1967) on the concept of transformations helps facilitate building a workable bridge between cognitive psychology and neurophysiology (Thatcher and John 1976).

Given this definition of cognition, it seems that language is a subordinate class of cognition in that it involves the initial transformation of sounds and patterned visual information (phonemes, morphemes, words, sentences) into elementary internal representational systems. Subsequent manipulations of these representations (e.g., comparisons to memory, semantic categorization, and the use of syntactical structures) are performed to create more complex levels of information representation.

Neural representational systems

It is generally agreed that environmental information is first transduced at the peripheral sensory level into neural space-time activity, which is subsequently transformed into internal representational systems (Perkel and Bullock 1968, Szentágothai and Arbib 1974). That is, there are general mapping processes in advanced organisms by which elements in the external world are represented or mapped onto elements in the internal milieu. In terms of information theory, a representational system is defined as any structure for which the elements are mapped onto, symbolize, or correspond to the elements of some other structure (MacKay 1970). The physiological mechanisms underlying the formation of neural representations are not completely known; however, recent symposia published in the *Neuroscience Research Programs* have reviewed this area and have attempted to establish conceptual guidelines (Szentágothai and Arbib 1974). For instance, Szentágothai and Arbib proposed an action-oriented, hierarchical organization of perceptual and memory processes in which an animal actively synthesizes new models and updates old models of the external world. In this regard, the updating process most likely involves matching and mismatching of representational models with sensory input (Thatcher 1976).

Changes in the early components of the human-scalp evoked potential often correspond to changes in the physical attributes of sensory stimuli such as intensity, contour, density, color, and spatial frequency (Regan 1972). The longer latency components of the human-scalp EP are often insensitive to the specific content of evoking stimuli provided subjects are attentive and processing information. For this reason the EP is often partitioned into an early or "exogenous" process, sensitive to the physical features of sensory stimuli, and later or "endogenous" process, sensitive to higher-level functions related to attention, decision making, and second-order information processing.

Linguistic information processing can be understood as afferent information transformed by specialized nerve endings into coded impulses that are conducted centrally. The physical features of the sensory stimulus (phonemes in the case of auditory input and lines, edges, angles, etc., in the case of visual input) are mapped onto a neural representional system. Various neurophysiological models can be used to explain the mapping process (Hubel and Wiesel 1962, Pribram 1971, Barlow 1972). Most of these models rely on feature extraction. That is, neural elements respond optimally only to a particular feature of the sensory stimulus. Feature extraction models are usually hierarchical (Barlow 1972) in that there is a hierarchy of levels of greater complexity both of the feature extraction and the representational systems. There are a few nonfeature extraction models (see Gibson 1969, Schwartz 1977) in which the anatomy of the brain uniquely determines mappings of the external world onto neural representational systems. For instance, Schwartz (1977) elucidated a conformal sensory map based explicitly on anatomy. He demonstrated that a logarithmic spiral on the periphery (on the retina or skin surface) is mapped as a straight line in the cortex. According to this model, perceptual phenomena such as size invariance and rotational invariance are inherent to the way peripheral receptors are connected to the cortex. In any case, whether feature extraction models or nonfeature extraction models eventually prevail, the concept of transformation of environmental patterns of energy into internal representations is fundamental to the field of neurolinguistics as it pertains to cognition and language.

Formal operations versus content of operations

In order to understand evoked potential analyses, it is important from the outset to distinguish between the neural representation of information and the neural operations performed on that information. This distinction is emphasized by Piaget (1971a, b) in his discussion of adaptation and the development of formal operations. In this context a formal operation such as logic can be invoked in a variety of circumstances, all of which may involve different information inputs (e.g., there are numerous possible syllogistic statements). Thus, the formal aspects of an operation, such as those involved in logic, are invariant over time, whereas the content being operated upon changes. In language, grammatical structure can be likened to a formal operation, whereas meaning may be considered the content. Another example is the act of remembering versus the content of the memory. Similar distinctions can be made for a wide range of cognitive operations such as, imagination, information comparison, image rotation, linguistic translation, and mathematical operations. At any given moment the operation and the content of the operation are inseparable; but these two features can be distinguished experimentally by the fact that the *content varies over time, whereas the operation is invariant.* This distinction is particularly relevant to the study of the electrophysiology of language since operations involving information manipulations and comparisons can contribute to recorded electrical activity. A primary question in evoked-potential studies is: *does an electrophysiological event reflect the specific content of an operation, or does it reflect a general operation that is invariant while content changes?*

Primary versus secondary representational systems

Chomsky's (1965) elegant formulation of transformal grammar led to a hypothesis of universal linguistic capacities, i.e., cognitive capacities that are specific and unique to language. Alternative views, however, are concerned with universals advocating universal cognitive capacities that are fundamental to all perceptual and cognitive experience but are not specific to language *per se* (Thatcher 1976, Greenfield 1976). An exhaustive analysis of these contrasting views is beyond the scope of this summary; however, a useful approach to understanding this issue is to first consider the distinction between primary representational systems and secondary representational systems.

Primary representational systems for both audition and vision are defined as the internal neural representation depicting the elementary features of a sensory stimulus (Thatcher 1976, Thatcher and John 1976). For example, natural speech stimuli are made up of vowel and consonant sounds, which form phonemes. In this case the primary representational systems reflect the processes by which the elementary features of speech stimuli (phonemes) are received.

Secondary neural representational systems map the larger and more meaningful units of languages such as morphemes, words, phrases and sentences. In this regard the secondary representational systems reflect the more holistic units of language. Another distinction is that the primary systems involve more phylogenetic histories (i.e., anatomical and inherited), whereas the secondary systems involve more experiential history or memory.

Are there primary representational processes specific or unique to language? This question is answered, in part, by studies using artificial synthesis of speech sounds (Liberman et al. 1967, Liberman 1970). Work by Liberman and his colleagues at the Haskins Laboratory revealed two important aspects of speech perception. First, speech sounds are perceived *categorically*. In nonspeech conditions a human observer can discriminate among many more stimuli than he can label or identify, but in speech perception this does not occur. That is, speech discrimination is no better than identification (see Lisker and Abramson 1964b). A second discovery by the Haskins group (Liberman et al. 1952, 1967) was that speech sounds violate the assumptions of perceptual linearity or invariance. That is, an invariant sound segment can represent different phonemes in different contexts or, conversely, a single phoneme can be represented by different sounds in different contexts. This work shows that the basic units of language involve representations with unique characteristics.

Recent EP analyses have provided correlates of categorical perception in neonates (Molfese et al. 1976). The latter studies demonstrate that neonates exhibit different average EPs to different speech sounds as well as marked hemispheric asymmetries. These studies, when considered as a whole, support the notion that language perception involves unique primary representational systems and that these systems are innate and functional at birth.

To what extent does language involve unique secondary representational systems? There is no definitive evidence for unique secondary representations as yet. It is clear that the left cerebral hemisphere is more important in language comprehension and production than the right cerebral hemisphere. It is not clear, however, whether this reflects lateralization of universal cognitive operations, unspecific to language, or the lateralization of language operations themselves. For example, damage to the left temporal or left parietal lobes in adults results in a wide number of cognitive deficits and not simply linguistic ones (Luria 1966, 1973; Konorski 1967). As noted by Luria (1973) and Konorski (1967), left parietal-temporal damage interferes with general analytical functions including the ability to abstract, to perceive complex patterns, and to maintain auditory sequences. In line with these considerations, Thatcher (1976) and Thatcher and April (1976) suggested that a universal aspect of analytic function such as logic, language and mathematics involves memory match and mismatch. Some support for this was provided in an EP study wherein hemispheric asymmetries appeared to be related to the general operation of memory match-mismatch and not language content itself (Thatcher 1977b). Another universal cognitive function, suggested by Greenfield (1976), involves the structural principles of hierarchical organization. A hierarchical organization is an organization of levels whereby lower level units or subordinates combine to form higher level units or superordinates. Many aspects of emotion, perception, and memory are hierarchically organized. Language also exhibits a hierarchical organization whereby phonemes combine to form morphemes and morphemes combine to form sentences; or in language development, the earliest phonological units precede the first morphological units, which, in turn, precede the syntactic one.

Thus, the relationship between language and cognition is multileveled. Unique language representations may operate at the primary sensory level. On the other hand, it is likely that semantic and syntactic language functions are not unique capacities, but involve universal cognitive operations.

Evoked-potential correlates of language information processing

Lateralization and localization

Evidence for anatomical localization of linguistic information processing is provided in several studies. Brown et al. (1973, 1976) showed that EPs recorded from F3 and T3 (left frontal and left temporal) exhibit different waveshapes in response to physically identical words when the words are used in different speech contexts. Evoked-potential waveshape differences were significantly greater when recorded from the left hemisphere than from the right hemisphere (Brown et al. 1976). The waveshape differences were not due to increased variance and were stronger from F3 than from T3 derivations. It is not clear in these studies, however, whether hemispheric asymmetries reflect lateralization of unique language operations or a universal cognitive capacity unspecific to language. Teyler et al. (this volume) showed maximal EP differences in T3 and not F3 to similar sounding words with very different meanings. These differences were reduced to words that conveyed the same meaning but had different features such as words formed by upper- and lower-case letters (e.g., DOG versus dog). These findings suggest that invariant EP waveforms from T3 reflect invariant semantic information. Thatcher (1976) demonstrated EP amplitude and waveshape asymmetries to physically identical words representing synonyms or antonyms in a delayed semantic matching task. The interhemispheric asymmetries were maximal in posterior T5/6, P3/4, O1/2) regions but absent in anterior regions. A similar anterior-posterior localization of lateralized EP processes was noted in a paradigm requiring subjects to extract identical meanings from words presented in two different languages (Thatcher 1977b). As mentioned previously, it is unclear whether these asymmetries reflect unique language capacities or universal cognitive operations.

Correlates of syntax

Syntax refers to the way in which words are put together to form phrases and sentences. Brown et al. (1973) examined EP waveforms elicited by identical words that terminated different phrases. For example, they examined EPs elicited by the word "fire" in the phrases "sit by the fire" and "ready, aim, fire." The verb produced a different EP than the same word used as a noun. Teyler et al. (1973) used a similar paradigm but examined EPs elicited by click probes that followed the word presentation. Teyler et al. (1973) reported that EP amplitude and waveform differences were dependent on the meaning and syntactic context of the preceding word. Recently, Brown et al. (1976) used an EP paradigm in which both the trigger word and the phrase were the same, e.g., they used the phrase "it was/led/." In this case the subjects were instructed prior to the phrase presentation to interpret the last word of the phrase as a verb ("the horse was led") or as a noun ("the metal was lead"). Clear EP waveform differences elicited by the last word of the phrase were noted in F3 when the word was differently interpreted in the two conditions. Although these studies demonstrate clear EP differences to physically identical words, it is difficult to determine whether the differences are due to the different meanings of the words or the different syntactic contexts.

Recently, Friedman et al. (1975a) examined EPs elicited by words comprising a sentence. They found clear differences between EPs elicited by articles, words representing the object of the sentence, and the last word of a sentence. The most pronounced effect was observed in EPs elicited by the last word of a sentence, which resulted in an increased latency and an enhanced amplitude of the late positive component (P400 process). The latter experiment had less confounding between word meaning and syntax than was evident in the previous studies since the meaning of the word and its syntactical function were counterbalanced. Friedman et al. (1975a) suggested that the EP changes noted to the last word of the sentence reflected the process of "syntactic closure."

Correlates of semantic information processing

Semantic refers to the meaning of representational content of a word or phrase. Several experimenters have investigated this aspect of language using evoked-potential analyses. Very few if any have successfully overcome the problem noted earlier about separating the content of an operation from the operation itself. For example, Teyler et al. (this volume) showed that words with the same meaning but different physical figures (e.g., DOG versus dog) elicit very similar EPs. On the other hand, words that are physically similar but possess different meanings (e.g., cut versus cup) elicit different EPs. A similar phenomenon was observed by Johnston and Chesney (1974) using an ambiguous figure that could be interpreted as a 13 or a B and by Grinberg and John (reported in Thatcher and John 1976) using a vertical line that could be interpreted as a number or a letter. In the latter studies general operations related to number versus letter operations were not controlled. In the case of cut versus cup, EP differences may have been due to verb versus noun operations.

The distinction between content and a general operation where the operation is invariant and the content changes is a subtle but important distinction. This distinction is best investigated in studies that control a given cognitive operation while manipulating content. For example, the contribution of content versus general operations in the studies such as by Brown et al. (1973, 1976) and Teyler et al. (1973, this volume) may possibly be resolved by averaging EPs to groups of verbs and groups of nouns and showing different EP waveforms (or clusters) within the verb or noun categories as a function of word meaning. If there are no differences within categories, then the differences between the categories may reflect a general process distinguishing the noun versus verb operation. It is still unclear, however, whether these operations are uniquely linguistic.

One of the most successful experimental distinctions between an operation and the content of an operation was provided by Chapman et al. (1977 and at this conference). These workers averaged EPs to six different semantic categories of words, based on Osgood's (1964) "Evaluative (+,-)," "Potency (+,-)," and "Activity (+,-)" dimensions, presented in random order. Subjects sat passively and observed the words without making an overt decision. The central idea was to make semantic meaning within a category invariant while randomly changing the physical characteristics of the word. In this way variations due to word features should cancel out while invariant responses, as a function of semantic category, should summate. Chapman et al. (1977) found that the average EPs to each of the six semantic word categories were markedly similar. When a Z-transform was performed on each EP data point by comparing the grand mean of all six categories to the EP means of an individual semantic category, then very marked difference waves were noted to occur. Normalized Z-differences for each of the six categories were markedly stable and replicable as demonstrated by discriminant analysis of an independent sample wherein EP semantic categories were differentiated with 55% accuracy. A chance result using six categories would be 16.7%. Results of experiments by Chapman et al. (1978) indicate that semantic content is reflected in slight variations or deviations from average latency and amplitude of the evoked response. Walter Freeman (1972, 1975) has been a strong proponent of precisely such a model where information is represented by phase deviations from an invariant reference process. Another interpretation of Chapman's findings, suggested at the conference, was that Z-differences could be due to arousal and emotive inequalities existing between semantic categories. There were six different categories indicating six different arousal or emotive states, however, which strains the classical definition of arousal. If the number of word categories were to be expanded and replicable Z-differences remained in each category, then the state interpretation becomes largely synonymous to semantic information. In any case, Chapman et al.'s findings indicate that the averaged EP is strongly influenced by general operations whereas the content of the operations may be reflected in deviations about the mean.

Summary

Several studies have demonstrated EP correlates of language information processing. These include evoked responses to elementary phonemic and syllabic speech sounds in children and adults, differentiated evoked responses to physically similar words with different meanings, and similar evoked responses to physically different words that convey the same meaning. Evoked potential correlates of syntax and semantics have been observed as well as some evidence of hemispheric lateralization and localization of cognitive functions.

Although these studies show that various aspects of language can be profitably studied with EP procedures, this survey indicates that clear distinctions between general cognitive function and specific language capacities are difficult to draw. Language appears to be unique primarily in the coding of the elementary aspects of speech stimuli. Higher levels of information transactions such as those involved in semantics and syntax are most likely specializations of universal analytical or cognitive operations. General cognitive operations such as abstraction, comparison, symbol sequencing, the extraction of inter- and intra-modal invariances, and the formation of hierarchical structure are extensively involved in language. These operations, however, also occur with nonlinguistic information.

DISTINGUISHING LINGUISTIC AND STIMULUS EFFECTS

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The application of evoked potential methods to linguistic research entails the presentation of auditory or visual stimuli. Physical characteristics of linguistic stimuli such as intensity, brightness, duration, length, and rise time must be carefully controlled as in other areas of ERP research. Other acoustic characteristics such as formant frequencies or consonant transitions uniquely identify sounds as speech signals that convey linguistic meaning. Stimulus parameters, both specific and nonspecific to speech, which must be considered in evoked potential studies of language, are reviewed in this paper.

General stimulus parameters

Much previous evoked potential research has focused on the effects of simple acoustic manipulations on the amplitude, latency, and waveshape of evoked potentials. Future research on the physical aspects of language should be designed in light of past findings. For this reason, it is important that stimuli be carefully described. The number of graphemes (visual presentation) or phonemes (auditory presentation) should be stated. All stimuli should be of the same length or duration, or subtend the same visual angle unless one of these elements is the variable under study (Taurozzi 1973). The loudness or brightness of stimuli should be matched (Picton et al. 1970). The rise time of acoustic stimuli should be specified since this variable may affect the auditory evoked potential (Lamb and Graham 1967, Lindsey 1971, Skinner and Antinoro 1971).

All of the physical factors contribute to waveform differences between stimuli. If the independent variable under study is not one of these variables, research that fails to control such factors may be seriously confounded. Given the influence of these stimulus characteristics on the evoked potential waveform, a detailed description of the physical parameters of the stimuli should be provided in the published report. For example, if auditory linguistic stimuli are employed, sonographic records should be included.

The manner in which stimuli are produced is an important factor. Use of a parallel or series speech synthesizer permits precise control of the speech signal. On the other hand, present computer models of speech lack many features that characterize natural speech, although such features may not be necessary for simple identification. The role of these cues has not been investigated. If natural speech stimuli are employed, a great deal of control may be lost. For example, while the onset of one formant transition in relation to other formants may be manipulated using computer-generated speech sounds, such manipulations are greatly limited when natural speech is used. In both cases, with natural and synthetic speech, it is important to control peak or average intensity levels, rise time, and stimulus duration.

A question could be raised concerning the legitimacy of averaging across stimuli differing in these characteristics. If stimuli do differ in some of the factors discussed above, should they be collapsed together? AEPs elicited in response to stimuli differing in rise time would be expected to differ. If these responses were then averaged, one would expect that variability would increase. Experimental designs should be examined for possible confounding of physical parameters of the stimuli with linguistic experimental conditions to avoid the possibility of a false finding.

Given the literature on habituation effects, order of presentation and the interstimulus interval (ISI) are of critical importance. By varying the ISI and presenting stimuli in a random order, habituation effects can be reduced (Regan 1972). ISI duration is another factor that should be considered. Enough time should elapse between stimuli to allow the background EEG to return to its prestimulus baseline level. This factor appears to vary with the age of the subjects tested. Latencies of EP components in younger subjects are longer than those for older subjects. Consequently, return to baseline takes longer in the younger group (Barnet and Lodge 1967, Ohlrich and Barnet 1972, Callaway and Halliday 1973).

Acoustic determinants of speech perception

Research on the perception of speech signals provides a direct approach for distinguishing between linguistic and cognitive functions (Liberman 1970). Given the variety of speech sounds employed in the world's languages (Ladefoged 1971), speech sounds appear to a great extent to be arbitrary elements restricted only by the dimensions and characteristics of the human vocal tract. These sounds constitute a perceptual, as well as a productive code for individual languages (Liberman et al. 1967). Such sounds can be broken down into basic units, many physical characteristics of which have been identified (Stevens and House 1972). These include acoustic bands of concentrated energy called *formants*, rapid *transitional* elements, and *voice onset time* (VOT). Vowel identity is generally signaled by the frequencies of the lower three formants in a speech sound, and consonant information is conveyed by the VOT cue and by an interaction of a rapid frequency shift (transition) with the formant frequencies. The precise role, however, of these cues in speech perception is not completely understood.

One issue in speech perception centers around the inability of a human language listener to detect changes in the acoustic signal until these changes cross a boundary that differentiates one speech sound from another. This perception of speech sounds is quite different from the ability to detect small changes in the frequency of a pure tone. Although adults are able to discriminate many more tones than they are able to identify or name, the ability to detect changes in consonant sounds is only as good as the ability to assign a unique label to these sounds.

The ability to discriminate only those speech sounds that can be labelled uniquely is called *categorical perception* and is thought to be due to VOT (Lisker and Abramson 1964b) and/or onset of the first formant transition (Stevens and Klatt 1974). Voice onset time refers to the relation between laryngeal pulsing and consonant release. A number of studies (cf. Liberman et al. 1967) have demonstrated that adults classify bilabial stop consonants with VOT values of 0 and +20 msec as /b/, and those with VOT values of +40 and +60 msec are identified as /p/. Adult English speakers fail to discriminate between sounds with VOT values of 0 and +20 msec or between those with VOT's of +40 and +60 msec. Both sets contain a 20-msec difference between pairs. These adults are able to detect a 20-msec change when it crosses the phoneme boundary. Intriguingly, native adult speakers of Spanish are unable to detect this difference between +20 and +40 msec VOT. Although Spanish does not use this boundary to distinguish speech sounds, it does make use of one between -20 and 0 msec VOT. This boundary cannot be detected by native monolingual English speakers. Thus, some speech cues appear to be used to discriminate and identify speech sounds in general (e.g., formants and transitional elements), and others, such as VOT, are specified by the language itself.

Preliminary use of EP procedures to study VOT perception appears encouraging. Molfese (1978) recorded auditory evoked potentials from T3 and T4 scalp locations from 16 adults who were involved in a phoneme identification task. Sixteen series of four randomly arranged bilabial stop consonants (0, 20, 40, 60 msec) differing only in VOT were presented to subjects who were instructed to press one telegraph key if they heard the syllable /ba/ and a second if they heard the syllable /pa/. Averaged AEPs were submitted to a principal components analysis (after Chapman 1974a), and four factors, which accounted for 91% of the total variance, were isolated. Independent analyses of variance identified two factors (Factors 1 and 4) that were sensitive to VOT changes across but not within phoneme boundaries. Both effects occurred only for the T4 lead, as can be seen in Fig. 1. A similar effect was found in studies involving 4-year-old children (Molfese and Hess, 1978) and 4-month-old infants, but not newborn or premature infants (Molfese and Molfese, in press).

While the frequency relations between the first three formants provide an invariant cue for vowel identification, no such invariance has been found for consonant

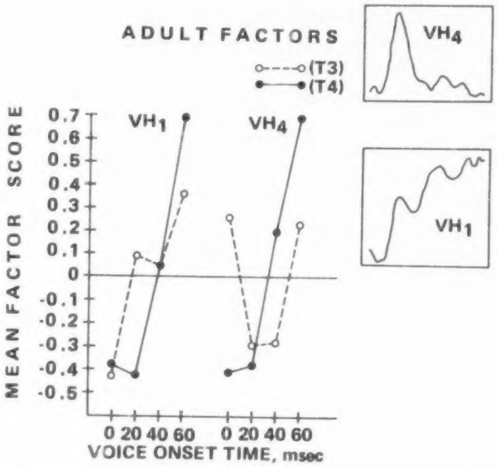

Fig. 1. Changes in mean score for Factors 1 and 4 as a function of VOT and hemisphere. The means for the dependent variable in the analysis of variance (the weight for the factors for the different stimulus conditions) are plotted along the ordinate. The stimulus values are plotted on the abscissa. Factor scores are plotted separately for left hemisphere (T3) and right hemisphere (T4) recordings. The temporal pattern of factor loadings is shown in the boxes on the right where time is plotted along the abscissa.

sounds (Liberman et al. 1967). Rather, it appears that the consonant transition changes as a function of the vowel context. For example, the consonant transition that carries information concerning the /d/ in the syllable /di/ is characterized by a rising second transition, and the consonant in the syllable /du/ is marked by a rapidly falling transitional element. In both cases, however, the initial consonant transition is identified as /d/. This issue is yet to be resolved by speech scientists.

The acoustic cues used to differentiate between speech sounds may become more readily identifiable through the application of EP procedures. Research in this direction by Molfese et al. (1976) entailed recording AEPs from sixteen 2-day-old human infants in response to a series of acoustic stimuli, which varied in formant bandwidth and presence of a transition. The stimuli are presented in Fig. 2. The two stimuli in the left column are perceived as: top, the speech syllable /gae/ characterized by initial transitions followed by steady-state formants and, bottom, a vowel syllable /ae/, which does not contain a transition. These sounds contain formants of normal bandwidth. The stimuli in the right column contain narrow bandwidth formants (sinewave). Again, the top stimulus contains a transitional element, but the bottom does not.

AEPs were recorded from T3 and T4 referred to linked earlobes. Averaged AEPs submitted to a principal components analysis yielded four components, which accounted for 96% of the total variance. Analyses of variance identified one component as reflecting changes in bandwidth and another as reflecting the presence or absence of formant transitions. These results suggest that evoked potential techniques may be sensitive to systematic changes in acoustic parameters related to speech perception. The question of acoustic invariance in consonant recognition still remains; perhaps these techniques could be applied to seek an answer.

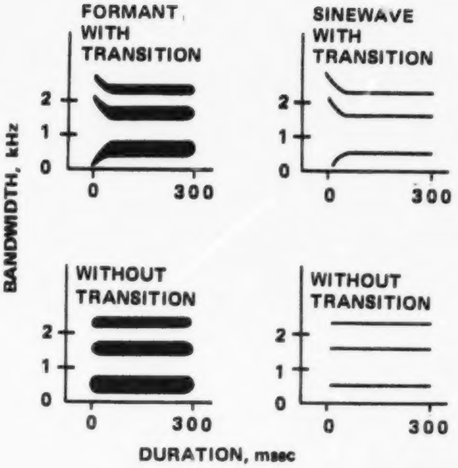

Fig. 2. Acoustic structure of syllables /gae/ and /ae/. Stimuli with normal width formant structure are on the left of the figure, and those with narrow band formant structure (sinewave) are on the right. Stimuli with transitional elements (consonant-vowel syllable) are presented at the top of the figure; steady-state syllables (vowels) are at the bottom. (Reproduced with permission from Molfese et al. 1976.)

LATERAL ASYMMETRY OF EVOKED POTENTIALS AND LINGUISTIC PROCESSING

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Introduction

Numerous behavioral studies using the dichotic technique (reviewed by Kimura 1967) and tachistoscopic recognition procedures (reviewed by White 1969) pointed to the inequality of the cerebral hemispheres in processing verbal and nonverbal information. With the advent of commissurotomy for relief of intractable seizures, studies of the "split-brain" human added to our knowledge of hemispheric specialization of function (reviewed by Gazzaniga 1970 and Nebes 1974). Recent anatomical evidence has shown that the cortical mass in the region of the planum temporale (Wernicke's area) is larger on the left than on the right hemisphere in both infants (Witelson and Pallie 1973) and adults (Geschwind and Levitsky 1968, Wada et al. 1975). That the brain's electrical activity would mirror these behavioral and anatomic asymmetries was a natural assumption for evoked potential researchers to make.

Early researchers in this area used repetition of the same or different stimuli with no task imposed upon the subject (e.g., Cohn 1971) or used discrimination paradigms (e.g., Morrell and Salamy 1971, Wood et al. 1971) where phonemic information was necessary to perform the task. With the exception of Molfese's data (Molfese 1975), results of these studies have shown extremely small amplitude asymmetries. Furthermore, many of these studies could be faulted on methodological grounds (see Friedman et al. 1975a).

Recent studies have attacked the evoked potential-language problem from a meaning or "deep-structure" level. Thatcher (1977a) employed a semantic match-mismatch paradigm, while Teyler et al. (1973) and Brown et al. (1973, 1976) used the same word in different meaning contexts. Friedman et al. (1975b) and Shelburne (1972) utilized a modification of the information delivery paradigm where subjects had to know the meaning of a linguistic unit in order to solve the problem. Although Friedman et al. (1975a, b), Galambos et al. (1975), and Shelburne (1972) found no consistent amplitude asymmetries, Teyler et al. (1973) and Thatcher (1977a) did. Brown et al. (1976), using stepwise discriminant analysis, found greater discrimination over the left hemisphere than over the right of evoked potentials elicited by the physically identical word in differing contexts.

Difficulties in assessing the significance of reported asymmetries

Analytic methods

While amplitude measures are straightforward and allow identification of discrete peak effects, analyses that focus on only a few points of the waveforms may be inappropriate if the evoked potential reflects changes in processing over time. Some investigators (e.g., Chapman, this section; Brown et al. 1976; Thatcher 1977) have, therefore, used whole-wave analyses, such as factor analyses, stepwise discriminant functions, and correlations. These kinds of analyses have an advantage in that they take the whole wave into account (i.e., all the sampled points), but have some difficulty in handling artifacts, such as latency shifts between waveforms. Ideally, one should use both amplitude measures and whole-wave analyses in drawing conclusions. This issue is complicated since the way one measures often leads to as many different results as there are measuring techniques, as well as difficulties in comparing results across studies.

Existence of lower-order asymmetries

The investigator demonstrating an asymmetry to a linguistic stimulus cannot immediately conclude that linguistic processing accounted for the asymmetry. For example, Davis and Wada (1974) have shown that asymmetries exist to lower-order stimuli, such as clicks and flashes with no task imposed upon the subject. Further, in data from my laboratory, we have seen the same direction standing asymmetries to linguistic as well as nonlinguistic stimuli, even after switching amplifiers to control for gain effects. Most of the more recent investigations (e.g., Brown et al. 1976, Wood 1975, Thatcher 1977a, Friedman et al. 1975a) are based upon an information processing approach. Thus, it would be extremely important to use a "noninformational" control and not simply a "nonlinguistic" stimulus as a baseline from which to measure asymmetric effects. Thatcher (1977a) used this kind of control by employing random dot configurations during intertrial intervals. Friedman et al. (1975a) used a "no task" control as a baseline condition, in which the subject simply listened to the stimuli without a task. Thus, the evoked potential researcher who wants to demonstrate an asymmetric effect due to linguistic processing must have evoked potentials elicited by noninformational control stimuli with which to compare evoked potentials in response to experimental stimuli with respect to both direction and magnitude of asymmetry.

Task and subject variables

Evoked potential studies of hemispheric lateralization have not as yet employed tasks that unequivocally involve semantic processing and/or are of sufficient difficulty to tap more than automatic aspects of language function. This, in part, has probably accounted for the paucity of robust evoked-potential effects. Approaches toward the goal of "sufficient processing" have been made (e.g., Thatcher 1977a, Brown et al. 1976). We should also design experiments that more closely approximate the real world of speech processing using, for example, connected discourse, since this is natural for human beings and ensures involvement of the language processor. Another possibility would be to use tasks and stimuli known to involve a good deal of competition between the hemispheres, since the tasks we do use may not engage the hemispheres differentially.

A related issue is the cognitive style of each subject. Each person is unique and engages in different methods for processing the same information. Thus, one subject might process a stimulus (which the investigator specifies as "verbal") in a nonverbal way, while another might process the same stimulus using verbal coding. Note Brown's discussion of individual differences elsewhere in this section.

The influence of task variables (coding strategies) on behavioral asymmetries has been demonstrated by Seamon and Gazzaniga (1973) who asked subjects to code a visually presented word by either subvocally rehearsing it or by generating an imaginal representation. In the rehearsal set, probes to the left hemisphere yielded significantly faster reaction times than probes to the right, while the reverse held for probes to the right hemisphere when subjects were in an imaginal set. Additional evidence for the influence of coding strategies comes from a study by Bever and Chiarillo (1974), which showed that musically sophisticated listeners recognized simple melodies better from the right ear than from the left, while musically naive listeners showed the well-known left-ear effect (see Kimura 1967). This evidence indicates that it was the kind of processing applied to the musical stimulus that determined which hemisphere was dominant. Thus, musically sophisticated listeners were able to organize the melodic sequence "in terms of the internal relations of its components" (an analytic or left-hemisphere function), while musically naive subjects organized the melodic sequence in a gestalt (a right-hemisphere function). These results suggest that the task assigned to the subject will have at least as strong an effect as the type of stimulus.

Difficulties inherent in averaging

Since we must repeat stimuli in order to obtain an average, we may "wash out" effects that are present in the single trial. For example, the repetition of the same word, whether or not in a different context, may lead to semantic satiation. Thatcher has proposed the use of "light averaging" (N's of 12 or less), and Friedman has suggested the scoring of single trial data (especially in P300 experiments) as done by Ritter et al. (1972). An alternative approach is the use of several different words with no repetition (cf. Chapman 1974b, this volume). Thatcher (this volume) has also pointed out that differences in skull thickness and volume conduction idiosyncrasies may affect the degree to which evoked potential techniques can resolve asymmetries at the scalp.

An additional problem is the interindividual variability that exists in the location of cortical landmarks (see Whitaker and Selnes 1976), as well as ambiguity in the location of the classical speech reception area (Bogen 1975). Thus, we may not be able to assume that we are recording from the same anatomical area in each subject. This is further confounded when one uses only two electrodes or averages across subjects.

The assumption has also been made that a voltage difference across the head implies a functional specialization difference between the hemispheres, i.e., that greater voltage implies greater output from the cortex over which the scalp electrode lies. Vaughan and Ritter (1970) using a volume conduction model and Kelly et al. (1965) have suggested that this may be an erroneous assumption.

Assumption of a unilateral processor

We still work under the assumption of a strictly lateralized language processor, although Gazzaniga (1970), Nebes (1974), and Zurif (1974) have shown that the right, so-called "nondominant" hemisphere is capable of receptive language function. Zurif, in fact, has shown that some processes necessary for decoding meaning are carried out exclusively in the right hemisphere. Thus, we may be washing out asymmetric effects by using stimuli and tasks that involve simultaneous, but differential, processing by the two hemispheres.

Summary

Whether evoked potentials can reflect lateralized functional processes is an unsettled issue. Contradictory findings can be partially explained by differences in stimuli, tasks, and analytic methods. Although asymmetries do exist, it is difficult to determine whether observed differences are related to linguistic or lower-order processing. More stringent controls and tasks directly related to speech reception are necessary to reduce "subject option" and to ensure that the hemispheres are engaged differentially.

Acknowledgments

I would like to thank my colleagues Walter Ritter and Richard Simson whose critical thinking contributed to some of the ideas expressed in this paper.

INDIVIDUAL DIFFERENCES AND SIMILARITIES IN LANGUAGE EFFECTS ON EVOKED POTENTIALS

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There is general agreement in evoked potential research on humans that common perceptual experiences, cognitive processes, and behavioral responses of different individuals produce similar effects on the waveform, amplitude, or latency of the average scalp-recorded evoked potential. Increasingly finer-grain cognitive processes have been demonstrated to have correlates in the evoked electrical activity of the brain, as exemplified in current research on EP correlates of language processing. Studies of the effects of linguistic meaning on EPs are beginning to approach the electrophysiological study of the mental activity that we subjectively experience as thought.

The question arises, then, at what point will we begin to deal with EP idiosyncracies due to unique experiences, cognitive styles and strategies, and thought processes of each individual? EP morphology may well be like a fingerprint: the gross structure is similar for most individuals, but the fine grain is idiosyncratic. As one investigates more complex levels of cognition, both the mental processes and their electrophysiological correlates should be increasingly unique for different individuals. For example, factors that might lead to idiosyncracies in EPs to language stimuli would be: small differences in the perception of stimulus meaning due to variations in cognitive speed or processing time, variability in the anatomical structure or physiological localization of language functions, and unique memory storage or retrieval systems.

Individual differences or similarities in the effects of language processing on EPs are essentially an empirical question. The P300, particularly to linguistic stimuli, has been shown to be very similar for different subjects (Shelburne 1972, 1973; Friedman et al. 1975a,b; Thatcher, 1977b; Kutas and Donchin, this volume). For example, Friedman et al. demonstrated that most subjects produce a larger P300 to the last word of a paced sentence, despite the fact that the information of the sentence was delivered several words earlier. Shelburne (1973), however, demonstrated an important difference in P300 to the last letter of CVC trigrams between children who performed well compared to those who performed poorly on a reading task.

Hemispheric asymmetries in the amplitude or latency of EP components to language versus nonlanguage stimuli have also been shown to be similar for the majority of right-handed subjects (Matsumiya et al. 1972; Morell and Salamy 1971; Cohn 1971; Wood et al. 1971; Buchsbaum and Fedio 1969, 1970; Neville 1974). An obvious source of subject effects in this type of research would lie in differences in the degree of left lateralization of language function. Subject differences in the asymmetry of EPs to language stimuli thus would be expected when comparing left- and right-handers. Molfese et al. (1975, 1976) has demonstrated that similar amplitude asymmetries in evoked potentials to language and nonlanguage stimuli can be seen in records from infants, children, and adults. Molfese has also reported similar effects on average EPs between infants for the presence or absence of a transition in a synthesized speech stimulus, the bandwidth of the stimulus, and the hemisphere being recorded. A subject difference was demonstrated in terms of an EP correlate of the sex of the infant. Thus, the research on EP correlates of the lateralization of language functions has generally demonstrated similar effects for the majority of subjects, with possible exceptions due to the effects of handedness and a nonlateralized correlate of sex in the response of infants.

Individual difference or similarity is particularly relevant in studies of EP correlates of language meaning. Are the EP effects of word meaning similar for different subjects? Teyler et al. (1973, Roemer and Teyler 1977) found that responses to a click preceeding the expression of the word "rock," for example, were dissimilar depending on whether the subject meant "a rock" or "to rock."

Although across-subject averages showed noun-verb differences, the characteristics of response to the two-word meanings appeared to be idiosyncratic. This was particularly true for the verb meaning of the stimulus homophones. Brown et al. (1973, 1976; Marsh and Brown, 1977) employed similar homophone stimuli in sentence or phrase contexts to demonstrate EP waveform differences to noun and verb meanings. Brown et al. (1976) specifically tested the question of intersubject similarity using multivariate statistical procedures. Separate EPs for the two-word meanings for each of 15 subjects were submitted to stepwise discriminant function analysis (SWDA) in an attempt to find common EP time points at which responses to noun and verb forms of the stimulus could be discriminated reliably. A discriminant function was derived from left-hemisphere responses, which identified EPs from the two conditions with 77% accuracy; but differences were not apparent from right-hemisphere responses. Thus, intersubject commonality in EP correlates of contextual meaning was demonstrated. Subsequently, similar analyses were done in an attempt to discriminate subaverages of five stimuli within single subjects. Although left-hemisphere responses could be reliably sorted by noun or verb meaning of the stimulus, there appeared to be little similarity between different subjects in the specific time points chosen for the discriminant functions. Thus, there was some degree of idiosyncracy in responses to different word meanings.

Perhaps the strongest case for intersubject similarity in EP correlates of language meaning comes from the work of Chapman et al. (1977, 1978). These investigators have demonstrated EP correlates of general semantic meaning as it is measured by Osgood's Semantic Differential scale. EP waveforms to groups of words occupying opposite polar positions on one of the meaning scales differed in the presence or absence of a specific component. Components differentiating EPs to words from the two categories were sufficiently similar for different subjects that average responses to similar words from different subjects could be reliably sorted with a template-matching procedure.

Intersubject similarity in the experiment of Chapman et al. might have been expected on several grounds. First, Osgood's scale represents perhaps the most general classification of semantic meaning. Second, it is constructed on the basis of intersubject similarities in the ratings of general semantic meaning. Finally, Chapman et al. averaged across individual words from a specific category, and thus may have averaged out idiosyncracies in responses to specific lexical meaning of words.

Comparison of the results of Teyler, Brown, and Chapman indicates that intersubject difference or similarity in EP correlates of language meaning is a matter of the level of linguistic-EP analysis. If one could observe the EP to a single presentation of a word in some ongoing linguistic context, the responses would have definite idiosyncracies due to the uniqueness of thought, imagery, and association of different people, or of the same person listening to the same message at different times. Perhaps this explains the failure of Teyler, who used averages of only 10 responses, to find similar meaning-related waveform differences between subjects, or of Brown to demonstrate similarity in EP discriminators within single subjects using averages of only five trials. As responses to the same word are averaged across a large number of contexts (either stimulus or mental), the response for individual subjects might be expected to approximate a generalized representation of the brain's response to word meaning. Since the function of words is to express similar meaning to people who speak the same language, one might expect similarities between subjects to increase above the single trial or small N level. Thus, Brown et al. were able to find intersubject similarities in the correlates of word meaning when comparing averages of 100 responses to the same word. Finally, as one averages across multiple presentations of different words from a single semantic class, demonstrated to be stable among individuals and cultures, one would expect intersubject similarities to emerge as demonstrated by Chapman and his colleagues.

This analysis ignores important differences in experimental designs used by different investigators. Nevertheless, it provides a reasonable synthesis of the results on the issue of individual differences and similarities in the effects of language meaning on averaged evoked potentials. This issue certainly merits further investigation.

CONTRIBUTIONS OF LINGUISTICS AND OTHER DATA BASES

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Neurolinguistics, the study of brain and language, has been spawned in an era of interdisciplinary research interest. The degree of interdisciplinary activity, however, may be more theoretical than real. Most neurolinguists are reformed physiological psychologists. Thus, current workers in the field come from the physiological as opposed to the linguistic or cognitive tradition. This is understandable since a general surge of interest in "more complex events" is prevalent in the neurosciences. We reflect a portion of this scientific evolution. We all agree that increased contact with other disciplines would be beneficial for this fledgling field, and, presumably, cross-fertilization would occur as well. Various data bases are presented, and the achieved or potential cross-fertilization is discussed in this essay.

Linguistics

Linguistics is the study of the structure of languages. Attention has been focussed primarily on formal description of grammatical regularities. Whereas most effort in neurolinguistics emphasizes phonemic, word, or semantic aspects of language, linguistics is primarily concerned with more global aspects of language. The most comprehensive theory of language structure is the generative grammar proposed by Chomsky (1965) and others as a set of formal rules capable of describing the relationships found in language. It is not and was not intended to be a model for biological aspects of language. Thus, there has been less interdisciplinary communication than one might assume. As the neuroscientist begins to deal with syntactic relations in more complex verbal contexts, the relationship to formal linguistic theory should become clearer. Conversely, our activities at elementary levels of language may trigger a resurgence of interest in these aspects of language on the part of linguists.

Psycholinguistics

Psycholinguistics can be defined as the study of how language is used and acquired. Neurolinguistics, at present, is concerned with brain correlates of language use, either production or reception. The interface here is better developed and has already proved fruitful. Still, most psycholinguists, like linguists, are not primarily concerned with simple elements, but rather with the relationships between elements at relatively complex syntactic, semantic, and organizational levels. Psycholinguists deal extensively with the uses of language as do neurolinguists, and the prospects for continued interaction are bright. We can aid the psycholinguist today in studying brain correlates of categorical perception across species and in further clarification of the localization/lateralization issue.

Psycholinguistic theory has emphasized the development of models more from a psychological than from a biological point of view. What would be most valuable for neurolinguists is a psycholinguistic theory of language acquisition and utilization that accounts for biological as well as psychological factors and has the formal precision of Chomsky's approach. Admittedly, this is a tall order.

Many psycholinguists feel that the single best insight into language behavior can be obtained from studying language acquisition. It is remarkable that, while there are individual idiosyncrasies in language acquisition, the overall developmental pattern is markedly similar. These commonalities hold across cultures and for handicapped (deaf) children as well. This invariance in language development may well be attributed to the underlying biological maturation and specialization of brain tissues. This area may be extremely fruitful for the future interface between brain and language research.

Clinical neurology

Clinical neurologists are interested in disturbances of language behavior (aphasias) due to brain pathology. Correlations between structure and function, although imperfect, offer a means of studying the brain in relation to language behavior. In addition, clinical neurology, of all the disciplines interested in brain and language, is most versed and concerned with the underlying biology, brain structure and function.

The lack of good correlation between pathology and disturbance is not unexpected because language behavior is undoubtedly not the consequence of activity in any single brain area. While it is probably true that many brain areas interact in language behavior, it is undeniably true that the anatomy and physiology of the brain are directly related to language. Our goal might well be the study of these interrelationships between areas of the brain. The task is complicated by the inadequacy of our tools and paradigms and by our not knowing where to look (or not being able to look, e.g., subcortically). To compound the problem, most pathological symptoms are not exclusive to language behavior, but involve other cognitive processes as well (see below).

In neurolinguistics we have no animal models. For a biological science, this is a severe handicap because most tools of the trade are invasive and inappropriate for human subjects. Complicated and unclear as they are, human suffering from "natural" lesions may offer a model for examining biological aspects of language.

Clinical neurologists interested in aphasia have developed theories and specific predictions usually related to localization of function. Although the theories are highly controversial and often rest on inadequate data, they are, in many cases, amenable to test by neurolinguistic techniques. Conversely, we may be able to devise clinical tools to aid in the differential diagnoses of brain damage.

Neurobiology

Interactions with neurobiology (the study of the nervous system) are well established. In one sense, neurolinguistics is a subspecialty of neurobiology. There is good evidence that the acquisition of language and brain maturation are closely linked. Since language is acquired by means of interactions between organism and environment, it may be safe to assume that there are concomitant changes in neuronal relationships similar, if not identical, to neuronal plasticity as studied in other contexts. Since we cannot directly study the mechanisms of these neuronal alterations but must rely upon electrical manifestations, we will have to depend heavily on neurobiology for the elucidation of the mechanisms themselves. Neurobiology, being a more molecular discipline, will probably contribute more to neurolinguistics than the converse. The contributions can potentially arise in many areas: an understanding of the neuronal (or nonneuronal) generators of the electrical signals we record, the underlying anatomy, the nature of physiological events in association cortex, and principles of feature extraction. Provided with these contributions–for example, in understanding the neuronal processes underlying feature extraction–it will be our job to extend them theoretically and functionally to the neuronal mechanisms involved in language behavior.

Cognitive psychology

There is probably no human brain pathology that disturbs language behavior without affecting other cognitive functions. The brain is an integrated organ. Psychobiology tells us that a good deal of integration occurs at virtually all brain loci. Language behavior is the complex intersection of sensory, perceptual, memory, syntactic, and semantic relationships. In language behavior, the brain is engaged in a dynamic process presumably involving widespread neuroanatomical loci. It is not unreasonable to assert that language behavior employs brain processes common to many forms of sensory, perceptual, memory, and other cognitive functions. It is a substantial challenge to neurolinguists to disentangle (if possible) those interactions to examine the degree of either overlay of functions or the specificity of certain brain processes in language behavior.

Many cognitive psychologists are using brain recording techniques in addressing questions that may be basic or at least related to language behavior. Thus, cognitive psychology and neurolinguistics appear to be entering an era of fruitful dialogue.

Other data bases

At least three other areas bear close relationships to neurolinguistics: ethology, developmental psychology, and the applied field of learning disabilities. To the extent that language behavior is an evolutionary extension of general communication schemes in animals, we may be able to learn from and instruct ethologists. Language, as a formal system, is specific to humans, but communication schemes are widespread. To what extent can parallels be constructed and brain processes be delineated?

The acquisition of language behavior, as mentioned previously, not only falls within the bounds of psycholinguistics, but, along with the development of other cognitive abilities, is a central theme of developmental psychology. We would be well advised to attend to the activities of workers in this area.

If neurolinguistics can offer a contribution to the condition of man in the near future, it will probably lie in diagnostic tools for the clinical neurologist in relation to brain damage and learning disabilities. While we have no delusions of offering remedies for these devastating human conditions, we can perhaps assist in the development of sensitive tools for the detection and classification of these conditions. Such a contribution would, by no means, be unappreciated.

METHODS OF EVOKED-POTENTIAL ANALYSIS IN LINGUISTIC RESEARCH

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The problems associated with methods of evoked-potential (EP) analysis do not appear to be different for the study of language and EPs than for other areas. Two aspects of relating EP effects to language variables, however, foster a sense of urgency in developing EP measurement techniques. One aspect is that in addition to focusing on linguistic variables, it is necessary to consider many other variables, both lower-order, such as sensory, motor, and artifact, and higher-order, such as general states and cognitive processes. Consideration of these additional variables is necessary to demonstrate specific relations between language variables and EPs. This tends to promote experimental designs with a large number of conditions and to promote EP measurement techniques that can separate EP effects related to the various classes of variables.

Another aspect that lends urgency to developing EP analysis is the relatively small size of EP effects associated with linguistic variables. Small EP effects do not mean they are not important. If we were simply trying to explain EPs, then starting with large EP effects would make sense. If we are seeking EP effects related to particular variables such as linguistic ones, then we need to use techniques that focus on these relations and be satisfied with reliable relationships whether they involve large or small EP effects.

At an early stage of research, a reasonable approach is to use techniques that assess general EP differences between conditions. At later stages, one wants to know more about specific differences. If an EP peak amplitude is reliably different between conditions that reasonably are related to linguistic variables, and not other variables, then useful information has been obtained. Negative findings are not as useful, however, because of problems in accepting the null hypothesis. What was the power of the statistical analysis? Was there a better EP measure that might have been made, perhaps another time point not at a peak? Was the peak measure not sufficiently stable, e.g., would a measure that incorporated information from several time points be more stable?

Another technique for more global assessment of differences between EPs is computing correlation coefficients. The common test of correlation significance based only on the number of paired observations (time points) is not appropriate since the amplitudes at all time points are not independent. Appropriate statistical tests can be found, however. For example, the correlation coefficients may be treated like any other measure for subsequent statistical test (e.g., t-tests, ANOVA) provided several r's are available per condition for assessing variability. Before averaging correlation coefficients or entering them into subsequent tests, the Fisher r-to-z transform should be applied. Used with appropriate procedures, correlations can be used to indicate overall similarities of EPs and similarity to a scoring template (e.g., Chapman 1974b; Chapman et al. 1977).

The most common measurement technique in EP research is to measure the amplitudes and perhaps latencies of various positive and negative peaks in EP waveforms. These peaks (e.g., P1, N1, P2, and P300) are often referred to as EP components and often implicitly assumed to be functionally singular entities. Such reification of manifest EP peaks may not be fruitful for understanding EP relationships in general, including linguistic ones. Most would agree that EPs are composites of a number of underlying components. Why assume that each underlying component corresponds to a manifest EP peak? The possibilities exist that several underlying components might contribute to a given peak and that a given underlying component might contribute to several EP peaks. These are empirical questions. Evidence for both of these possibilities has been found (Chapman 1974a; Chapman, et al., in press).

The use of multivariate analyses (e.g., John et al. 1964; Donchin 1966, 1969; Chapman et al. in press) may be of considerable help in EP analyses since it is concerned with multiple measures and with considering them in combination as a system of measurement. Two of these techniques, which have been used with EPs, are *factor analysis* and *discriminant analysis.* Among the several factor analytic techniques, the method of choice is often principal components analysis followed by an objective, analytic rotation, e.g., varimax method. Principal components analysis can be used to uncover and measure latent EP components, which are independent and may overlap at various time points. The measures of the latent components, in contrast to the original measures at each of the time points, are more parsimonious, have increased reliability (measurement stability), and may be used to measure the separate contributions to various time points. The relation of these latent components to the experimental conditions is a separate question that may be analyzed by submitting the component scores to other procedures, such as ANOVA or multiple discriminant analysis.

Discriminant analysis is another form of multivariate analysis, which can be used to relate EP measures, including latent component scores, to experimental conditions. It combines EP measures into functions that best discriminate the designated conditions.

In research on the connotative meaning of words, attention was focused on EP effects related to the semantic classes in a generalizable way (Chapman et al. 1978). Stable EP measures and relationships to semantic classes that were generally true for the entire group of subjects were sought. Because the EP waveforms of different subjects are reliably different from each other, EP data were standardized for each subject separately. Each subject's data at each time point were transformed to z scores (mean = 0; standard deviation = 1). These transforms removed the average EP waveform of each subject from further consideration, since individual differences were not of interest. By analogy, if we wish to measure the growth of trees, it is helpful not to include in our measurements the mountains on which they grow. Next, the standardized data for all subjects were combined in a varimaxed principal components analysis (Dixon 1975). This was computed to: (1) determine the EP components found in this semantic experiment and (2) measure the amount of each component in each EP. This approach provided more stable EP measures than using the raw amplitudes at each time point.

The next step was evaluating the extent to which these EP components contained semantic information. The latent component scores for all subjects were entered into multiple discriminant analysis (Dixon 1975) to develop classification functions that discriminated among the semantic classes.

A common set of classification functions was developed for all subjects, and their success provided one test of the generalizability of the semantic EP effects. The results were cross-validated by a jack knifed procedure, which assesses the classification success when each case is left out of the development set and then classified. The results were further cross-validated by applying the classification functions developed from EP data for one list of words to EP data for another list. The classification functions used various combinations of a number of the orthogonal EP components to distinguish the six semantic classes. Thus, one or two general EP components, such as P300 and CNV-resolution (Chapman et al., in press) were not sufficient to account for the dimensionality of the data.

In general, the answer to the question of the specificity of language effects depends on the dimensionality of EP measures. Multivariate analysis techniques can help us answer in an organized way the kinds of questions we want to ask about EP data and their relation to experimental variables. Of course, sophisticated data analysis cannot carry the burden alone. Data analysis can only meaningfully measure EP effects produced by experimental manipulation. It is paramount that experimental designs control variables of interest independently, or at least manipulate them to different degrees, to provide a valid data base for measurement.

EVENT-RELATED POTENTIALS ASSOCIATED WITH LINGUISTIC STIMULI: SEMANTIC VS LOWER-ORDER EFFECTS[1]

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Recent studies of event-related potentials (ERPs) have stressed the value of these measures as possible indicators of cognitive and linguistic functioning (e.g., Teyler et al. 1973, Brown et al. 1973, Johnston and Chesney 1974, Megela et al. 1977). This research has suggested that linguistic meaning can influence ERP waveforms, implying that semantic as well as sensory characteristics of stimuli may be reflected in electrophysiological recordings from the human scalp.

We designed an experiment allowing a more stringent test of the hypothesis that underlying processing of word meaning may be detected in the ERP. In this study, ERPs were recorded in two classes of words, synonyms (words nearly identical in meaning but different in physical characteristics) and homonyms (words identical in physical characteristics but different in meaning). If ERPs reliably encode linguistic meaning, then synonyms should elicit potentials with similar waveforms, and homonyms should elicit potentials with dissimilar waveforms. Since the P3 component is related to semantic and cognitive characteristics (Sutton et al. 1965, Friedman et al. 1975), while the N1P2 component of the ERP is related to sensory characteristics of stimuli, it was predicted that semantic meaning would influence the P3.

Method

Six right-handed females participated in the experiment. They were seated in a comfortable chair in a sound-deadening recording chamber and were instructed to remain alert and to avoid eyeblinks and body movements during presentation of stimuli. The experimental session lasted approximately 1 hour.

Scalp electrical activity was recorded by Beckman miniature Ag/AgCl biopotential electrodes mounted in a flexible lycra cap worn by the subjects. In three subjects, electrodes were placed over left and right frontal areas (at locations equidistant between T3, F3, and C3 for the left lead, and between T4, F4, and P4 for the right lead), and in the other three subjects, over left and right temporal areas (equidistant between T3, C3, and P3 for the left lead, and between T4, C4, and P4 for the right lead). These scalp placements may reflect activity near presumed language areas of the brain. Linked earlobes were used as reference, and a forearm electrode was used as ground. Eye movements were recorded by disk electrodes placed lateral to and underneath the right eye.

Stimuli were common nouns, equated for frequency and familiarity. Synonyms were rated as to degree of similiarity in meaning, and homonyms as to degree of difference in meaning by 30 students in an introductory psychology class. On the basis of these ratings, one synonym pair and one homonym pair were chosen to serve as stimuli. Short phrases were constructed with these stimulus words occurring in the last position of the phrase. Stimulus phrases are presented in Table 1. In addition, a short phrase identical to the synonym phase, but ending with a different stimulus word, was constructed to ensure that any ERP waveform similarities between synonyms were not due to the fact that the synonyms were preceded by identical phrases. All phrases were equated for number of syllables and were presented to each subject at the beginning of the experiment in order to make their meanings clear.

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Table 1. Stimulus Phrases

Synonym:	THROW THE SMALL	ROCK STONE
Homonym:	SHUFFLE THE WALK ON THE	DECK
Phrase control:	THROW THE SMALL –	BOOK

Stimulus phrases were tape-recorded in a random order, with 8- to 12-second interstimulus intervals. The phrases were then played to the subject through an overhead loudspeaker. Each phrase was presented 30 times. Although stimulus volume in the two ears can be affected by shifts in head position and thus can produce different ERPs from the two hemispheres (Regan 1972), the use of randomized stimulus presentations in this study makes it unlikely that the mode of stimulus presentation affected the results.

EEG was amplified through a Grass Model 7 polygraph with a bandpass of 1 to 75 cps and was recorded, along with pulses signalling stimulus onset generated by Massey-Dickinson programming equipment, on FM tape for off-line computer analysis. ERPs were obtained for stimulus words only. EEG was averaged at a sampling rate of 512 cps for 1 sec. In addition, product-moment correlations were computed between pairs of waveforms and for peak-to-peak and peak-to-prestimulus baseline amplitudes within the following time windows: 100 to 200 msec (N1P2) and 250 to 400 msec (P3).

Results

Correlational analyses

Correlations were obtained for each subject at each electrode site between the following stimulus pairs: synonym-synonym, homonym-homonyn, and synonym-phrase control word for each time window (N1P2, P3, and entire ERP). Correlations were also computed over the entire waveform between right and left hemisphere leads for each stimulus. These data are presented in Table 2 for both frontal and temporal leads. Each entry represents a mean correlation over three subjects. At all electrode sites, the highest correlations were obtained between the homonym pair, especially for the 250 to 400-msec time segment (P3). Correlations for other pairs show essentially random variation; the several positive correlations between synomyn 1 and the phrase control word may be attributable to the fact that these words shared a common final sound.

Table 2. Product-Moment Correlations between Stimulus Pairs for All Leads

	Left frontal			Right frontal		
Stimulus pair	N1P2	P3	Entire	N1P2	P3	Entire
Synonym 1-synonym 2	-0.32	-0.09	0.20	-0.19	-0.10	0.15
Synonym 1-phrase control	0.47	0.09	0.35	0.36	-0.04	0.22
Synonym 2-phrase control	-0.37	0.12	-0.10	0.09	0.04	0.04
Homonym-homonym	0.18	0.61	0.37	0.19	0.46	0.30
	Left temporal			Right temporal		
Synonym 1-synonym 2	0.18	-0.24	0.02	-0.05	-0.01	0.09
Synonym 1-phrase control	0.01	0.15	0.11	0.01	0.23	0.06
Synonym 2-phrase control	-0.26	-0.14	0.05	0.04	0.04	0.07
Homonym-homonym	0.20	0.46	0.34	0.37	0.43	0.23

Over the entire waveform, the mean correlations between hemispheres were very high, ranging from 0.61 to 0.74 for both frontal and temporal leads.

Correlations were transformed into z-scores (eight correlations per time segment per subject) and then analyzed by a three-way repeated measures analysis of variance (Dixon 1975) with electrode placement (frontal versus temporal) used as the grouping factor and stimulus pair and hemisphere used as repeated measures. For each of the three analyses of variance performed, results were similar. A significant main effect of stimulus pair was found (early segment: $F(3,12) = 4.87$, $p < .02$; late segment: $F(3,12) = 9.07$, $p < .002$; entire waveform: $F(3,12) = 4.44$, $p < .03$). Analysis of the mean z-transformed correlations showed that these were highest in all cases for the homonym-homonym comparison. No significant group (frontal vs temporal) or hemisphere effects were found.

Amplitude analyses

Peak-to-peak amplitudes of N1P2 and P3 were computed for each stimulus word at each electrode location for all subjects. These amplitudes were then analyzed by a three-way repeated-measures analysis of variance with electrode placement (frontal vs temporal) as the grouping factor and hemisphere and phrases as repeated measures. For the N1P2 components, a significant group by hemisphere interaction appeared: over all phrases, amplitudes at the left temporal lead were higher than amplitudes at the right temporal lead, $F(1,4) = 8.49$, $p < .05$. Similarly, for P3 components, left temporal amplitudes were higher than right temporal amplitudes, $F(1,4) = 11.28$, $p < .05$. Table 3 presents means and standard deviations of amplitudes at each electrode site for both early and late components. These results suggest that larger amplitude ERPs to semantic stimuli are evoked over the left temporal hemisphere than over the right temporal hemisphere. Since a nonlinguistic control group was not included in this study, however, it is unclear whether this finding represents a specific semantic effect or a generalized effect to all stimuli.

Table 3. Laterality Comparison of N1P2 and P3 Amplitudes (μV)[a]

		Left hemisphere	Right hemisphere
Frontal	N1P2	6.95 (2.18)	6.45 (1.69)
	P3	6.29 (1.42)	5.93 (1.82)
Temporal	N1P2	6.67 (2.97)	4.81 (2.59)
	P3	8.07 (2.6)	4.73 (1.57)

[a] Each amplitude represents the mean over three subjects. Standard deviations in parentheses.

Sample ERPs from two subjects are presented in Fig. 1. This figure shows the similarities between ERPs to homonyms, and the dissimilarities between ERPs to synonyms. Moreover, ERPs to the same stimulus recorded at left and right hemisphere leads had very similar waveforms.

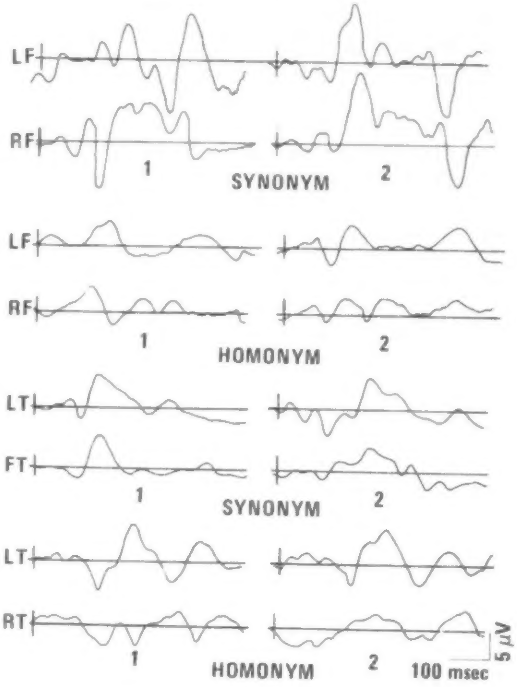

Fig. 1. Sample ERPs to synonym 1, synonym 2, homonym 1, and homonym 2 from frontal and temporal leads. Waveforms were traced from photographs of a computer slave screen. Note the similarities in waveshapes of ERPs to homonym pairs and the dissimilarities in wave shapes of ERPs to synonym pairs. Frontal ERPs are one subject and temporal ERPs are from a different subject. Vertical lines represent stimulus onset. LF: left frontal; RF: right frontal; LT: left temporal; RT: right temporal.

Discussion

This study demonstrates that lower order sensory effects, related to physical or acoustic features of stimuli, are more important than semantic effects in influencing ERP waveforms. ERPs were more similar between words of different meanings but similar physical characteristics than between words of similar meanings but different physical characteristics. These results held for both early (N1P2) and late (P3) components and for both frontal and temporal ERPs. Thus, ERPs may not provide a sufficiently sensitive metric to discriminate higher order semantic processing in a design where the subject is relatively passive and is not required to make cognitive or linguistic decisions. Future research on these questions should incorporate behavioural tasks designed to actively engage the language processing centers. For instance, Megela et al. (1977) reported a more reliable semantic effect on ERPs recorded in a habituation/generalization paradigm.

No significant hemispheric asymmetries at frontal scalp electrode locations were found. On the other hand, both N1P2 and P3 amplitudes over all phrases were larger over the left temporal hemisphere than over the right temporal hemisphere. These differences were not of large magnitude, although they were consistent across subjects and across individual stimuli.

In summary, it appears that consistent semantic effects on ERPs are difficult to distinguish. In these data, scalp electrophysiological activity was influenced predominantly by sensory rather than semantic characteristics of stimuli.

Summary

An experiment designed to test semantic influences on event-related potentials using synonyms and homonyms was performed. Correlational analyses between pairs of waveforms showed that consistent patterns were found between homonyms, while ERPs to synonyms were not significantly correlated. For all stimuli, both early and late components were of higher amplitude over the left temporal hemisphere than over the right temporal hemisphere. Future research on semantic correlates of ERPs should utilize paradigms requiring active linguistic processing by the subject.

VISUAL EVOKED POTENTIALS TO LANGUAGE STIMULI IN CHILDREN WITH READING DISABILITIES[1]

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Shelburne (1972, 1973) investigated visual evoked potentials (VEPs) to language stimuli in normal adults and children. In the 1973 study, normal children were presented letter stimuli in sequence as consonant-vowel-consonant (CVC) trigrams. The task was to decide whether the CVC formed a word or a nonsense syllable. When the child performed well on the task, VEPs to the third-position stimulus (last consonant in the CVC sequence) had greater positive amplitude than VEPs to first-position (initial consonant) and second-position (vowel) stimuli. If the child could not distinguish between word and nonsense syllables, no such difference in VEPs was found. It was suggested that VEP differences were related to the children's ability to make a correct decision in the problem-solving task.

Results from previous studies suggest children with reading disabilities (dyslexia) would perform poorly on the task and show no differences in VEPs from third-position stimuli compared to VEPs from first- and second-position stimuli. The present experiment was undertaken to test these hypotheses.

Methods

Nine male children aged 9 to 14 (mean age, 11 years) were paid participants in the study. Children with relatively pure reading disabilities (i.e., no evidence of neurological, sensory, or psychiatric handicap) were selected on the basis of evaluation by the Cincinnati Center for Developmental Disorders. Screening included complete medical history and physical examination, extensive psychological testing, speech and hearing evaluation, psychiatric and neurological consultation, and school achievement evaluation.

Testing procedures have been detailed elsewhere (Shelburne 1972, 1973). Visual stimuli consisting of white letters on a black background were presented sequentially to form consonant-vowel-consonant (CVC) trigrams. Each trial consisted of the presentation of blank-C-V-C-blank at fixed 1-sec intervals with a 3-sec intertrial interval. CVCs formed either words or paired nonsense syllables with the same first two letters as the word. Trial runs consisted of the randomized presentation of 50 words and 50 paired nonsense syllables. Subjects completed four runs and were retested in the same manner 1 year later.

The child was seated in a comfortable chair in a dark room. He was instructed to observe the letters during each trial and to decide whether or not the CVC was a word. After the second blank the child pushed a toggle switch to the right (word) or left (nonsense syllable). Immediate auditory feedback indicated whether the response was correct (tone) or incorrect (buzzer).

EEG was recorded using a 1.3-sec time constant at Cz, P3, and P4 referred to linked ears. During the initial session, eye movements were recorded between electrodes at the right outer canthus and below the right lower lid. Subjects were retested a year later. Vertical and horizontal eye movements were recorded separately during the second session.

VEPs for each position in the CVC trigram were averaged separately. 95% confidence intervals were also calculated for each point in the averages. Point-by-point comparisons between waveforms were performed to determine the latencies at which statistically significant (0.05 level) differences occurred. The criteria for scoring VEP differences for individual subjects was the occurrence of three consecutive points in averaged waveforms where the 95% confidence intervals of first- or second-position VEPs did not overlap with the third-position VEP. See Shelburne (1972, 1973) for further description of this method.

Results

No differences in VEPs for words compared to nonsense stimuli were observed. Subsequent comparisons were pooled across these stimulus categories. Fig.

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[1] Study supported by U.S. Public Health Services Grant No. HD05221.

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1 illustrates VEPs to first- and third-position stimuli in four dyslexic children. No consistent difference in VEP amplitude attributable to CVC position was observed in the learning disabled group. Table 1 shows performance scores and VEP latency differences observed in individual dyslexic subjects during the first session (runs 1-4) and second session (runs 5-8) recorded a year later. One subject (S.M.) was not retested. The results indicate some improvement in performance of six children during retesting, although the error rate of the dyslexic group (31.6%) was still high compared to that of normal children (12.1%).

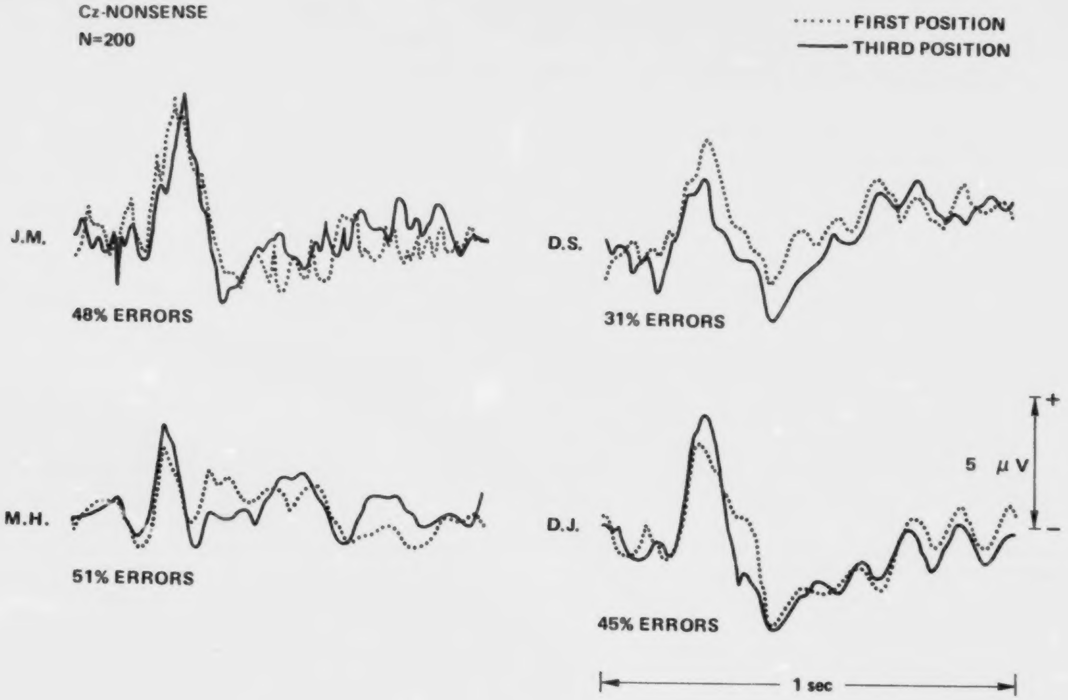

Fig. 1. Mean of 200 vertex VEPs to word and nonsense syllable stimuli in four children with reading disabilities.

Table 1. Individual Data for Children With Reading Disabilities

Subject	Age[a]	Runs 1-4		Runs 5-8	
		% errors	Latency window of VEP differences[b]	% errors	Latency window of VEP differences
D.J.	9	45	-	36	-
L.H.	12	25	-	11	-
D.H.	9	28	-	11	560-850
D.S.	14	30	-	22	-
O.J.	11	48	410-550	36	-
J.M.	9	48	-	49	-
L.B.	10	41	390-680	36	450-590
M.H.	11	51	-	52	-
S.M.	13	13	-		Not done

[a] Age at initial testing.

[b] Latencies define the beginning and end of the epoch during which significant VEP amplitude differences (third position > first or second position) were observed.

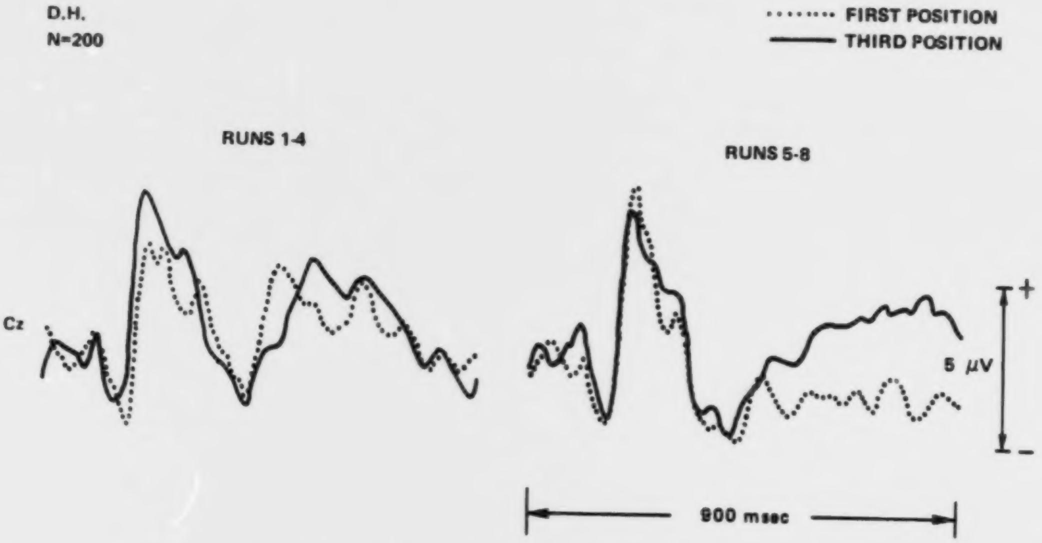

Fig. 2. Mean of 200 VEPs to word and nonsense syllable stimuli for subject D.H. Runs 5-8 were performed 1 year after runs 1-4.

The data of subject D.H. merit comment. Among the subjects retested, D.H. showed the greatest improvement (17%). This performance change was accompanied by the development of a first-third position VEP amplitude difference in the latency range 560 to 850 msec. This difference is clearly shown in Fig. 2.

Data from previous experiments with normal children (Shelburne 1973) were combined with data from dyslexic children. Subjects were then separated into two groups defined by the presence or absence of VEP differences, irrespective of reading ability. The mean percent errors was 7.6 for the group with VEP differences and 35.0 for the group without VEP differences ($t = 7.52$, $df = 32$, $p < .001$).

VEPs of two children (O.J. and L.B.) in the present study exhibited eye movement contamination (Fig. 3). Differences in averaged eye movement occurred at the same latencies as VEP differences. VEP differences listed in Table 1 for these subjects, therefore, can be attributed to eye movement artifact. Other dyslexic subjects showed very little eye movement. As a group, dyslexic children had a mean eye movement rate (measured grossly on the electro-oculogram) of 16/min compared to a rate of 25/min for normal children.

Discussion

Word and nonsense CVC trigrams were presented visually to children with reading disabilities. In previous experiments (Shelburne 1973), normal children who performed well on this problem-solving task showed greater positive amplitude of VEPs from third-position stimuli than VEPs from first- or second-position stimuli. With the exception of subject D.H. in runs 5-8, the reading disability children showed no significant VEP differences when eye movement artifacts were excluded. In contrast, 17 out of 20 normal children tested previously showed significant VEP differences. The absence of VEP differences in both dyslexic and normal children was associated with poor task performance. Dyslexic children as a group had far more difficulty than normal children in discriminating between words and nonsense syllables.

Eye movement contamination poses a serious problem in ERP research, particularly in VEP studies of children (Shelburne 1973). Analysis of eye movement patterns indicated that dyslexic children made fewer eye movements than normal children made during the task. Eye movement patterns may, in fact, provide a useful measure to differentiate children with reading disabilities from normal children who perform poorly on the task and show no VEP differences. The total number of eye movements and amount of EOG artifact appears to be less for the dyslexic than for the normal child.

Is there a causal relationship between eye movements and reading ability? Critchley (1964) and Goldberg and Arnott (1970) both concluded that faulty eye movement patterns were the result, rather than the cause, of reading disabilities. Reading disabilities

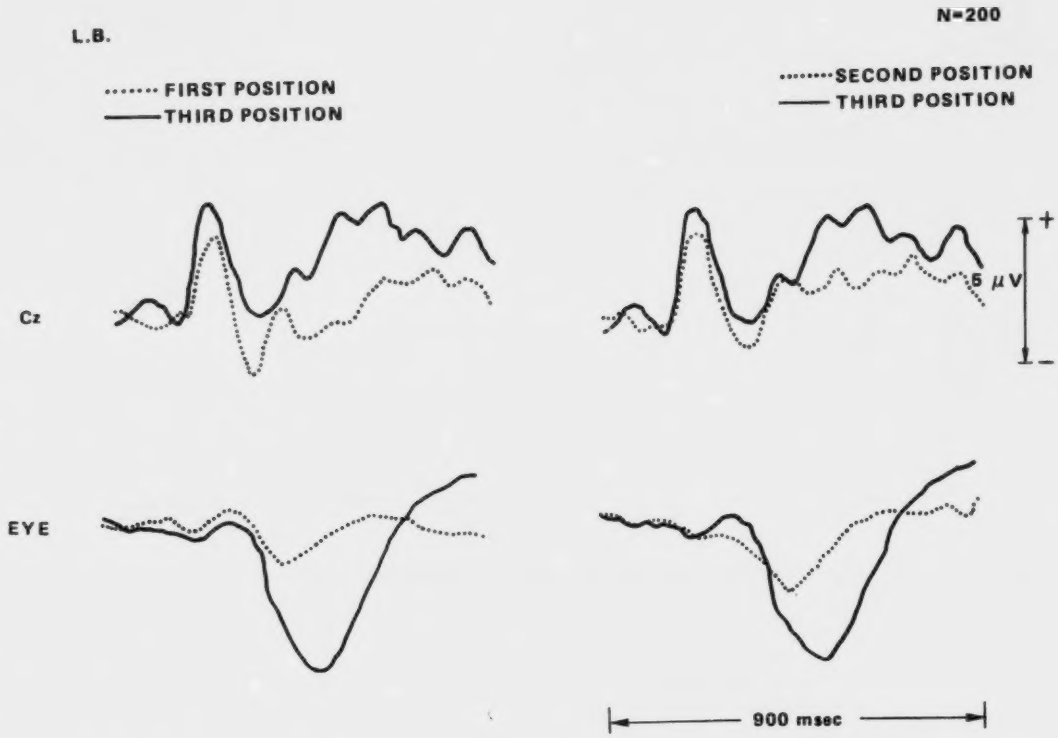

Fig. 3. Mean of 200 VEPs to word and nonsense syllables. Each channel is computer-averaged eye movement recordings from lateral canthus and infra-orbital ridge. Calibration for VEPs only.

become less apparent with time and remedial therapy. One subject (D.H.) showed improvement in performance associated with development of normal VEP differences after a 1-year interval. A much larger study of VEPs in children with reading disabilities is currently in progress.

Summary

Visual stimuli in the form of consonant-vowel-consonant (CVC) word and nonsense syllable trigrams were randomly presented to nine male children with specific reading disabilities (dyslexia). In previous experiments, normal children who could decide whether or not the CVC formed a word showed greater amplitude VEPs to third-position stimuli. This difference appears to be related to the subjects' ability to solve the problem and resolve the uncertainty. Children with reading disabilities were characterized by: (1) poor performance on the word task, (2) no VEP differences between third-position responses and first- and second-position responses, (3) low averaged eye movements, and (4) low total eye movement rate.

CHOICE OF ACTIVE ELECTRODE SITE AND RECORDING MONTAGE AS VARIABLES AFFECTING CNV AMPLITUDE PRECEDING SPEECH[1]

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Previous investigations concerning the electrophysiological correlates of language production have focused on two separate but related aspects of brain electrical activity: the motor potential (MP) and the contingent negative variation (CNV). The MP, which has received the bulk of research attention, was examined initially by Ertl and Schafer (1967) and Schafer (1967). Although these authors were able to record "nonrandom cortical activity" prior to onset of vocalization, they did not discuss their findings in relation to hemispheric dominance. Subsequently, McAdam and Whitaker (1971a) recorded similar potentials preceding speech, the amplitudes of which were asymmetrical. They presumed that the hemisphere showing the largest negative shift was the dominant hemisphere for speech and language. Their data have been criticized on methodological grounds by Morrell and Huntington (1971), Szirtes and Vaughan (1973), and Grabow and Elliot (1974). Grozinger et al. (1975) have examined in detail a number of these criticisms and concluded that with appropriate controls, interhemispheric asymmetries of brain potentials preceding speech can be demonstrated.

Assuming that the fixed foreperiod CNV paradigm might minimize artifacts introduced by preparatory changes in tongue position and throat muscle tone, Low et al. (1974, 1976) employed such a paradigm to evaluate differential hemispheric involvement in speech production. These authors conducted a series of studies involving 51 subjects (40 normals, 11 epileptics). Of particular interest are their data from the epileptics; in 10 of them CNV asymmetries accurately predicted the result of carotid amytal testing. Although the grouped mean differences reported by Low et al. for the normal subjects showed significantly larger shifts in the hemisphere contralateral to the preferred hand, they were careful to point out that not all the normals showed this relationship. Zimmerman and Knott (1974) reported larger CNV's preceding speech in the left hemisphere of 4 of 5 normal adults, whereas only 22% of a population of stutterers showed similar findings. Large left hemisphere CNV amplitudes have also been reported by Kostandov and Brilling (1973). Michalewski (1975), on the other hand, found only isolated incidence of left greater than right CNV asymmetries in 18 subjects.

In summary there appears to be some evidence both from MP and CNV studies to support the statement that there is an electrophysiological correlate of speech production which is consistent with clinically obtained data. A review of the literature reveals, however, several methodological differences with regard to the placement of both active and reference electrodes and the number of replications per subject. For example, the usual procedure has been to employ active electrodes at IF3 and IF4 referenced to linked mastoids with one recording session per subject. Low et al., on the other hand, favor an electrode placement termed "inferior-temporal" (T1, T2) referenced to contralateral ear. These procedural differences may reflect critical methodological considerations since the choice of active and reference electrode sites and recording montage have been shown to influence both magnitude and waveform of the averaged evoked potential (Goff et al. 1969). Furthermore, Low (personal communication) has found that in most subjects asymmetries increased in magnitude over repeated sessions. This is a particularly interesting observation since much of the evidence on test-retest reliability of the CNV is conflicting. For example, Cohen (1969) reported a correlation of +0.80 between two test sessions separated by 2 to 8 days using 34 normal subjects. Straumanis et al. (1969) reported a correlation of +0.20, whereas Roth et al. (1975) noted a median correlation of +0.68 between retests separated by from 5 min to 7 days.

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[1] Work supported by grants to Weinberg from Medical Research Council of Canada.

[2] See list of contributors for current address.

The present investigation was therefore designed to evaluate CNV amplitudes recorded from inferior frontal (IF3, IF4) and inferior temporal (T1, T2) sites employing both contralateral and linked mastoid references. Serial recordings were carried out to evaluate the contention by Low et al. that the asymmetries became more prominent with repeated recordings. Behavioral data were also collected from the subjects concerning dominant handedness (Annett 1967) and cerebral dominance for language (dichotic listening, Kimura 1967).

Methods

The six subjects were asymptomatic volunteers with no previous experience in a CNV experiment. Subject characteristics are given in Table 1. All subjects served in four recording sessions separated by 1 to 2 weeks. Due to technical difficulties in the final data analysis, data from only three sessions for each subject are presented.

Brain electrical activity and eye movements were recorded with a time constant of 5.0 sec and high-frequency cutoff of 30 Hz. Ag/AgCl disc electrodes were affixed at Cz, IF3, IF4, T1 and T2. Electrodes IF3 and IF4 were located 11 cm lateral and 4 cm anterior to Cz (McAdam and Whitaker 1971a) while T1 and T2 were placed 2 cm inferior to the bisection of F7-T3 and F8-T4, respectively (Low, personal communication). Pairs of similar electrodes attached to the left (A1, A3) and right (A2, A4) mastoid processes served as references. The reference combination A3 + A4 is subsequently referred to as linked (L) while A1 and A2 are the contralateral references. All interelectrode impedances were less than 2.5 kΩ. Beckman biopotential electrodes at the outer canthus and supraorbital ridge of the right eye referenced to L were used to record EOGs. EEG and EOG were digitized on-line and averaged over a 3.496-sec epoch. Eight artifact free trials were used in each average.

Subjects were positioned comfortably on a bed in a sound-attenuated chamber. A television monitor located approximately 4 m in front of the subject was used for tachistoscopic presentation of visual stimuli. In the word speak (WSP) and word button press (WBP) conditions, S1 was a 3- to 6-letter word presented for 50 msec followed 1500 msec later by a question mark (?), which served as S2. In the WSP condition, subjects were instructed to vocalize the word presented at S1 as rapidly as possible after S2. In the WBP condition, the subject pressed a button held in the preferred hand to terminate S2. In the standard (STD) condition, S1 was a 1000-Hz tone burst presented for 150 msec followed 1500 msec later by S2, a series of 10 c/s clicks, terminated by button press. Both S1 and S2 were presented via loudspeakers placed under the bed. In all conditions, the intertrial interval varied randomly between 5 and 30 sec. The three conditions were run twice on each experimental day with the sequence of conditions randomized across subjects.

Hand preference was quantified with a modification of the Annett questionnaire and scoring procedure (Annett 1967). The 12 test items concerning hand usage for various actions were retained and scored as +1 or −1 for right and left hands, respectively, while mixed usage was scored zero. The range of possible scores was +12 to −12.

Cerebral dominance for language was assessed twice for each subject with a dichotic listening task (Kimura 1967). Each test was separated by at least 2 weeks. Fifty sets of three pairs of digits from 1 to 10 (omitting 6 and 7) were recorded on tape with a 500-msec interpair interval and a 10-sec interval between sets (Neville 1974). The digits were presented through Hosiden stereo earphones connected to a Sony TC-270 tape unit. To control for possible auditory inequalities, subjects equated the intensity of 30 sec of white noise in the left and right earphones. In addition, the earphones were reversed for trials 24 to 48. The first two sets of digits were always practice trials. Subjects were instructed to listen to each set of digits and verbally report as many as possible, in any order, during the 10-sec interval. Responses that showed a left or right ear superiority were scored as +1

Table 1. Subject Characteristics

Subject	Age	Sex	Hand	Annett[a]	Dichotic 1[b]	Dichotic 2[b]
LAT2	22	M	R	+ 9	+ 1	+ 6
LAT3	25	M	R	+12	-17	-10
LAT4	21	F	R	+11	-12	-12
LAT5	21	M	L	- 5	-11	-10
LAT7	25	F	L	-12	-24	-17
LAT8	30	F	R	+ 8	-13	-10

[a] Annett values range from +12 to -12 with + values indicating preferential right hand usage.

[b] Dichotic scores have a possible range from +48 to -48 with - scores indicating right ear preference, i.e. left hemisphere superiority.

and −1, respectively. A zero was assigned if both ears were equally accurate. Scores were summated for each subject and could range from +48 to −48.

CNVs were quantified as the mean amplitude over the 200-msec interval prior to S2 relative to the pre-S1 baseline. These mean values were converted to μV by comparison to a 50-μV calibration pulse averaged in a manner analogous to the EEG.

Results

Fig. 1 is an overlay of the average CNV's obtained at each electrode in each condition across three experimental days for subject LAT 5. This subject was chosen for presentation as he shows a marked difference between IF3 and IF4 during the WSP condition. Hemispheric differences recorded from the remaining subjects were not as definitive in either direction.

Table 2 contains the grand mean and standard deviation of CNV amplitudes obtained at each electrode site. Repeated measures t tests and analysis of variance applied to the data showed only significant ($p < 0.05$) condition effects. As seen in Table 2, these differences are confined to a significant reduction in amplitude in the two-word conditions (WBP and WSP) as compared to the standard (STD). No significant differences were found between the WBP and WSP conditions. Additional analysis showed no significant day or electrode effects or interactions.

Table 2. Grand Mean CNV Amplitudes (μV) Obtained Across Subjects and Days for Each Electrode in Each Condition

Electrodes	Condition		
	Std	WBP	WSP
IF3-A2	-4.62 ±3.33[a]	-1.23 ±4.23	-1.87 ±2.98
IF4-A1	-4.86 ±3.40	-0.01 ±3.27	-0.38 ±2.89
IF3-L	-4.02 ±2.96	-2.88 ±3.57	-2.16 ±3.30
IF4-L	-2.98 ±2.74	-0.62 ±1.72	-0.07 ±4.22
T1-A2	-1.46 ±2.31	3.47 ±3.07	0.44 ±2.28
T2-A1	-1.54 ±2.84	2.49 ±4.25	0.60 ±2.70
CZ-A1	-17.45 ± 7.69	-9.45 ±4.09	-10.70 ± 4.77
CZ-A2	-16.78 ± 7.74	-8.78 ±4.49	-10.18 ± 4.58
CZ-L	-16.72 ± 4.41	-9.67 ±3.07	-11.11 ± 4.31

[a] Bottom line of each row is the standard deviation for each mean.

Discussion

Since CNV amplitude was not significantly different for linked and contralateral references, there appears at this time to be no reason for favoring one reference system over the other.

Furthermore, the data do not offer any uncompromising evidence for hemispheric differences in the CNV attributable to preparation for speech. Of the three subjects showing larger CNVs in the left hemisphere during speech production, two were left-handed; however, they both showed left-hemisphere preference in the dichotic listening task. That the same subjects showed consistently larger CNVs in the left hemisphere in both the WSP and WBP conditions suggests that these asymmetries are not related to speech production *per se*. Rather, the results may be peculiar to any paradigm employing a word as S1. The data presented by Weinberg et al. (this volume) support this suggestion.

Although the relationship between right-handedness and left hemisphere lateralization for speech is generally accepted, the nature of the relationship for non-right-handers and persons with mixed-handedness is unclear (Newcombe and Ratcliff 1973, Branch et al. 1964). Similarly, Briggs and Nebes (1976) have shown a high incidence of right-ear superiority for dichotic listening in a population of left-handers. As a result, *a priori* assignment of subjects into groups or data analysis performed on the basis of these variables may result in more artifact than fact. We propose that subsequent research would be more profitable if analyses were done first on a single-subject, single-trial basis. For each subject the direction, magnitude, and variability of any asymmetries would then be quantified. As a second step, single-trial data of all subjects could be subjected to a classification analysis to form groups based on clusters of dependent variables. Electrocortical variables relating to cerebral dominance for speech production would then be determined empirically rather than being forced into the mold of pre-existent assumptions. As was recently noted, perhaps we should be reasoning from the waveform outward rather than from the event inward.

This study definitely points to the necessity for further detailed investigation of the methodological considerations raised.

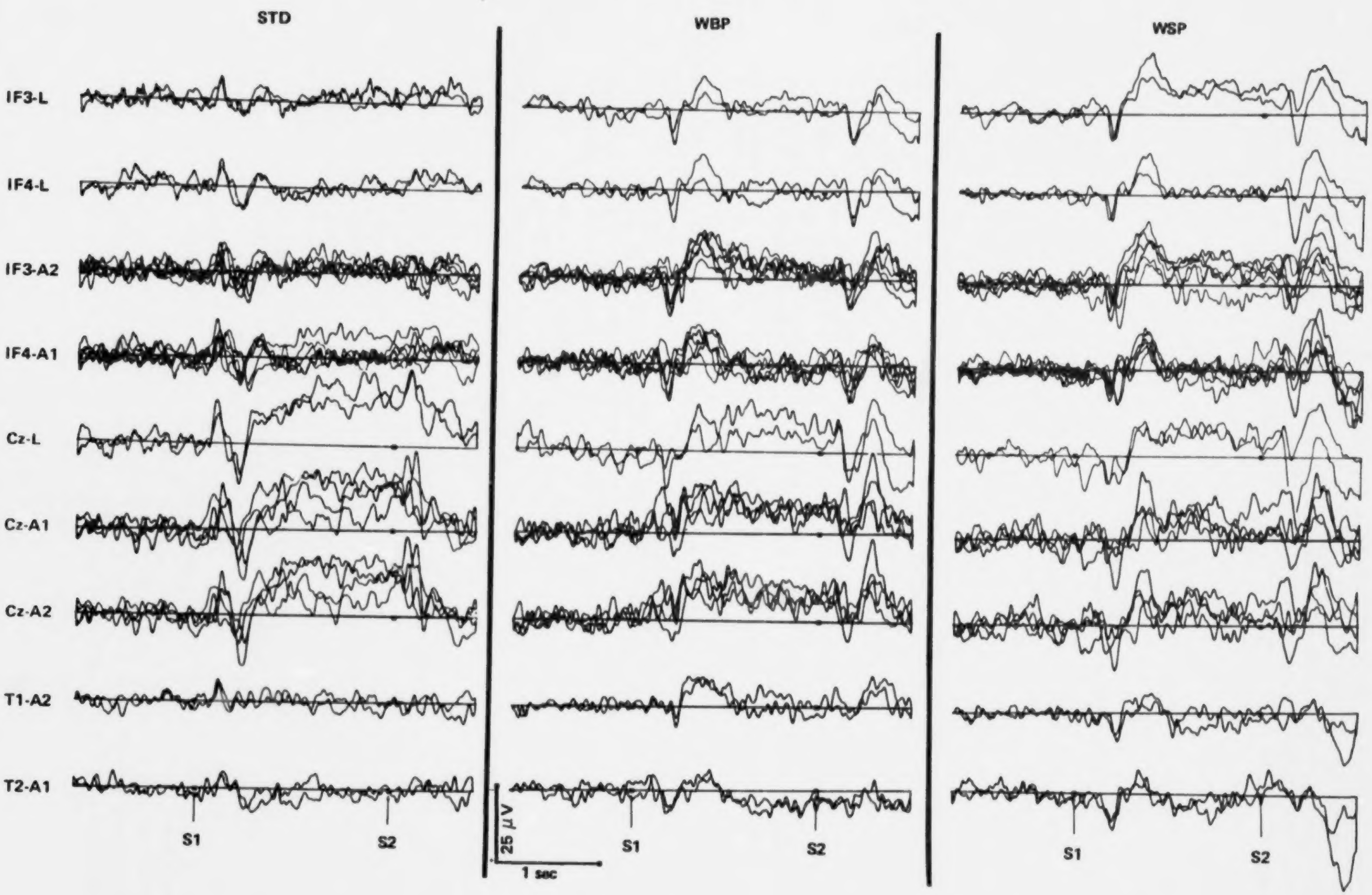

Fig. 1. Overlay of averaged waveforms obtained on successive runs for subject LAT5. Negativity at the active electrode is seen as an upward deflection. See text for location of reference electrodes.

Summary

CNV amplitudes were evaluated at inferior frontal and inferior temporal recording sites employing both contralateral and linked mastoid references in three different conditions. No significant hemispheric asymmetries were found when speech and nonspeech paradigms were compared regardless of active electrode site or reference montage. Significantly smaller CNV amplitudes were seen at all electrodes when a word was used as S1. The need for further methodological studies is emphasized.

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V. DEVELOPMENT AND AGING

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DEVELOPMENT AND DEVELOPMENTAL DISORDERS[1]

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This section is a summary of postconference correspondence concerning development as an independent variable in ERP research. An exchange of correspondence on development was solicited from a number of investigators taking part in the conference, as well as from some not participating. Those contributing to this correspondence are listed below:

1. J. Cohen, Northwestern University Medical School, Chicago, Illinois.
2. R. Dustman, Veteran's Administration Hospital, Salt Lake City, Utah.
3. B. Fenelon, University of Newcastle, New South Wales, Australia.
4. R. Halliday, Langley Porter Neuropsychiatric Institute, San Francisco, California.
5. H. Kohn, New Jersey Rutgers Medical School, Piscataway, New Jersey.
6. G. Lelord, Regional Hospital Center of Tours, Tours, France.
7. G. Marsh, Duke University, Durham, North Carolina.
8. C. Warren, Illinois Institute for Developmental Disabilities, Chicago, Illinois.

Discussion in the correspondence was confined to major problems that arise whenever the investigator injects change over age or maturation into an ERP study. Age takes on significance whenever processes are changing rapidly (as at the extremes of the life span), whenever age is a variable, or whenever rate, or lack, of development is of concern. Some investigators consider development a tool for the study of process and view it as lacking its own substantive information; from this viewpoint, the papers included in this section may seem more appropriate to other sections of this volume. Other investigators, in contrast, consider development *per se* as a substantive area of investigation in its own right, one that raises unique questions and provides useful information. However the investigator views this question, there are common problems that need to be considered. The following issues were posed as the framework for critical evaluation of development and ERP.

Issues

The paucity of developmental information

The main body of information concerns sensory-evoked potentials to relatively simple stimuli (Dustman et al. 1976, Ellingson 1968). Furthermore, most evoked potential data relate to infancy with little effort to collect data between age 2 and adolescence. Studies spanning middle and old age are also needed to complete the longitudinal picture. We need further longitudinal and cross-sectional studies of contingent negative variation (CNV), Bereitschaftspotential (BP) or readiness potential, and P300 that encompass the entire life span. The studies at this conference reflect a broadening of thinking and efforts. Such efforts are intimately related to the following issue.

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[1] Editor's note: This section, unlike others in the volume, did not emerge by design from preconference correspondence among selected panelists. The interest of ERP investigators in problems of development and its disorders, however, was clearly apparent from the spontaneous submission of the ten data papers assembled here. These papers were originally included in the psychopathology plenary session chaired by J.R. Knott and J. Tecce at EPIC IV. Dr. Karrer accepted the responsibility *ex post facto* of organizing and editing these papers. In order to provide some continuity with other sections, Dr. Karrer also undertook a postconference correspondence to define the critical problems of development, aging, and related disorders that might be amenable to resolution by ERP methods.

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Conceptual basis of developmental studies

Most developmental studies have been descriptive. While this approach is necessary and important, investigators need also to conduct studies that utilize predictions from known events in behavioral and neurological development. Such work could advance our understanding of the relationship between event-related potentials (ERPs) and behavior. For example, it would be of interest to relate the development of P300 to changes in cognitive growth. If current formulations about the significance of P300 for cognitive processing of stimulus events are correct, changes in size and topography should occur with the infant's cognitive development. Since P300 reflects subjective probabilities of events, it should reflect the infant's and child's development of hypotheses concerning event probabilities and expectancies (cf. Bower 1974, Stevenson 1972). Such an index would add specificity to our present generalized markers (e.g., eye movement, heart rate) of model building, habituation processes, and orienting of infant and young child.

As another example, consideration could be given to the question of whether the development of motor differentiation and skill lead to changes in the waveform and topography of the potentials that precede movement. These data have consequences for the interpretation of motor-related potentials and the interaction of their components. The P300 and motor-related potentials may prove clinically useful for the evaluation of cognitive and motor development in children or adults that challenge our present neuropsychological tests.

Since the study of ERPs is a major source of information concerning human brain function, it is necessary to establish their relationship to meaningful segments of behavior and to their neurological underpinnings. Questions concerning neurological development could be generated comparable to those posed for behavioral development. It would be of interest, for example, to know whether CNV is present in some form prior to or in the absence of the normal maturation of dendritic processes, e.g., in infants, mentally retarded, or sensory-deprived animals. Correlative studies of slow ERPs to known developmental data in humans may be fruitful.

Methodological issues

Useful developmental information is dependent on good methodology. In work with an infant or young child, the time spent in putting on electrodes becomes extremely critical. Since the attention span and "co-operation span" of the infant or child is short, the amount of data that can be collected in a single session is severely limited. Repeated recording sessions to collect sufficient trials for reliable waveforms are not always possible, particularly if one is dealing with an outpatient population. There has been some experimentation with electrode harnesses or helmets for quick and easy application, but the results have met with little success. Development of an effective and durable rapid-mount electrode harness would facilitate developmental ERP research.

A closely related problem concerns the limitations of restricting the subject by direct wiring of electrode leads to the amplification system. The innovative use of commercially available telemetry systems offers a possible solution to this problem.

More imaginative paradigms and stimulus events that can hold the infant's or child's attention during the trial are also needed. Such improved techniques would assist in controlling changes in state during the session and minimize movement artifact. Data recovery is usually about 50% or less with children and infants. How does this affect the interpretation of the data?

Variability

The amplitude of the average response is dependent upon both the amplitude and latency variability (jitter) of single-trial responses. That is, averaged responses are larger when variability is reduced. This factor is a major one in the large-amplitude evoked responses of Down's Syndrome individuals. The determination of variability requires trial-by-trial analysis. Since amplitude and variability are functions of underlying neural systems, some additional understanding of the neural systems is gained by considering both measures.

Sensory system function changes with age

At a given light intensity, the amount of light reaching the retina of a 70-year-old is about one-quarter of that reaching the retina of a 20-year-old. Some consideration should be given to determining sensory thresholds of subjects of different ages and adjusting stimulus intensities so that the effective intensity used across ages is reasonably constant. This factor may also be of importance when studying ERPs in certain patient or handicapped groups in whom generalized or specific sensory loss is suspected or known.

Discussion

The response, concepts, and recommendations that emerged in the postconference correspondence were focused on these problems and future directions of developmental ERP work rather than the critical evaluation of present or past work. This emphasis is in part due to the paucity of developmental ERP research. The next conference should foster a critical discussion of findings.

Conceptual issues

ERP investigators are fond of touting their techniques as a means of investigating the intact brain. Thus far, the validity of this assumption is more a matter of faith than empirical evidence. The value of the ERP in developmental research may lie in the fact that different components appear to be related to different features of cognitive processing and motor performance. ERPs should be considered an adjunct to anatomical and biochemical studies for obtaining information on the integrity of physiological and behavioral systems. Further ERP studies in animal models and clinical populations with known lesions, central nervous system dysfunction, or genetic anomalies should be undertaken to expand our knowledge of the brain mechanisms that underlie specific ERP components in humans.

Most developmental studies have been cross-sectional (cf. Cohen 1973, Dustman et al. 1976, Ellingson 1968). Evidence of the long-term stability of the ERP measures is lacking. That is, are the measures made at a single point during development predictive of measures taken later in the life span? Longitudinal studies that relate ERPs, particularly slow potentials, to anatomical, physiological, and psychological changes during development are needed. There is an increased interest in the relationship between ERP development and the plethora of information on cognitive (cf. Flavell 1977) and perceptual development. No reliable body of data relates ERPs to the development of functional abilities (e.g., reading, motor skill), much less to cognitive, perceptual, motor, or psychosexual development.

Parametric studies during development are essential. For example, variations in stimulus intensity can accentuate differences between normal and pathological development, differences which in turn may be related to the modulation of environmental input (Buchsbaum 1976, Galbraith et al. 1976, Karrer 1976). Stimulus intensity effects within or across modalities are dependent upon sensory threshold and the subjects' subjective magnitude function. Yet there has been no attempt to study this problem developmentally.

The need for parametric studies is demonstrated by Courchesne's finding (1977) of no N1-P2 differences between children (aged 5-8) and adults in a visual-attending paradigm. Since N1-P2 differences between attend and nonattend channels depend on a rapid presentation of stimuli (Schwent and Hillyard 1975), the ISI used by Courchesne (1250 msec) may not have been rapid enough to elicit developmental differences. In children, however, Courchesne observed large negative waves (30 μV) with latencies of 400 to 500 msec and large positive waves that peaked around 970 msec. These potentials, absent in adults, occurred only to novel stimuli and were frontally distributed. What the potentials signify in terms of development is unclear; parametric studies of late components and slow ERPs during development are needed to resolve this question.

It is an oversight that major changes in anatomy and metabolism during the early years have never been tied to ERP development. So far, the alpha rhythm and other bands have been the main variables studied. The only important findings to emerge from such studies are the breakpoint at about 3 months (when alpha starts) and the slow speeding of the rhythm. The full realization of these efforts will require better information on correlative anatomy. Such data would help, for example, to elucidate the mechanism underlying disparate latencies of ERPs recorded over homotopic sites in the two hemispheres. In addition, sensory deprivation and other experimental manipulations such as hypothyroidism (Eayrs 1971) in newborn animals result in well-known anatomical (reduced dendritic density) and biochemical changes. There have been no studies of concomitant effects on slow potentials that should theoretically be related to such changes, e.g., the presumed dendritic basis of CNV (McSherry 1973). ERP data from multiple sites, gathered in different laboratories, may provide norms relevant to the sparse information on dendritic development and myelination that could be related to retarded development.

Research on the normal development of ERPs in children should be directed to factors that have proved to be significant in the early development of the EEG itself. Factors of ERP topography, symmetry, and complexity are more germane in development than in the adult. The literature suggests that the function of CNS structure alters during early development and that the processes of myelinization and synaptic elaboration are major aspects of neural development. Rate of conduction and complexity of synaptic potentials are clearly correlated to, if not causal for, the ERP.

The development of paradigms that reflect normal behavioral growth and permit concomitant ERP recording is necessary to understand developmental disorders. ERPs would, it is hoped, shed light on the mechanisms underlying the disorder in question. For instance, myelinization deficiencies may result in slowed neural conduction creating a nonoptimal temporal confluence of CNS activity and, consequently, long ERP latencies. Presently, there is insufficient information for other than the crudest interpretation of possible deviant responses in patients. It is imperative to determine means and standard deviations of amplitude, waveforms, and latencies over the life span in order to detect differences associated with learning disability, brain trauma, infectious disorders, toxins affecting the brain, and demyelinating disease.

While the papers in this section clearly show that various ERP measures in developmentally disabled children are different from those found in normal children, there is no evidence concerning the reliability or reproducibility of these differences. Studies of interhemispheric differences related to skill deficiencies, handedness, and cognitive development are also necessary (see Fenelon, as well as John and Prichep, this volume). Evoked response patterns of individuals may be idiographic to the extent that different conditioning histories, variations in perceptual and cognitive strategies, and motivation affect them. Group data may yield only general nomothetic features of ERPs; nevertheless, normative studies provide the empirical basis for defining differences in the ERP patterns of aberrant populations.

Behavioral techniques presently can "discriminate" developmental syndromes better than ERP measures. While there is disagreement on the diagnostic role of ERPS, it seems that these highly technical, complicated and unvalidated procedures are mainly appropriate for sensory problems (e.g., color vision, acuity in certain subject populations, brainstem EP for the auditory pathway), problems not easily assessed by other means. The relationship of ERPs, psychometric, and neuropsychologic measures should be examined.

We tend to treat experimental manipulations as though they were synonymous with the labels used to characterize them. A current favorite is "attention." Three recent studies of auditory EPs in hyperactive children (Halliday et al. 1976, Prichep et al. 1976, Hall et al. 1976) have manipulated attention, although the experimental procedures used were different in each case. It may well be that all these studies tap the same process, but that remains to be seen. One way around this equivalence problem is to record ERPs while varying task difficulty. Such an approach has a better likelihood of unraveling the relationship between cognitive abilities and changes in brain states.

Methodological issues

Electrode application fatigues some children and uses up precious experimental time. Helmets and other headgear seem to increase rather than decrease experimental time. Three methods of electrode application were recommended: bentonite and cotton balls, collodion, and electrode collars with surgical tape. (Data on the comparative effectiveness of these methods is not available.) Anxiety and boredom may be reduced by free play between recording conditions or the use of cartoons and TV programs. These strategies may serve as reward at appropriate times or be an integral part of the experimental paradigm.

Selection of subjects on the basis of skill and behavioral maturation criteria may provide a greater payoff than selection based on chronological age, IQ, or clinical category. Most studies concerned with developmental abnormalities focus on comparisons between pathological and age-matched normals. While these comparisons are often informative, it may be difficult or impossible to predict *a priori* which variables within the normative population are most critical to "control." For instance, it may not be sufficient, depending on the question asked, to match for age alone when the experimental population includes mental retardates. The experimenter may need to control for mental, as well as chronological, age—which means that two separate *control* groups may be required. Similar problems exist with the behavioral and physiological parameters that may be of interest. Pathological groups differ on many variables, and it is difficult to specify what the observed ERP differences represent. One recommended procedure is, first, to define general groups (e.g., retarded of age x and IQ y), even though these groups may be too heterogeneous, and then to sort on the basis of performance in the ERP task (e.g., fast RT or slow RT, low threshold or high threshold). This further sorting provides a more homogeneous and functional grouping that allows better analysis of the ERP-behavior relations and of the aberrant vs. normal development data. One can determine if a normal subject with slow RT is similar to a retardate with fast or slow RT. The measures obtained (e.g., topography, amplitude, and latency) may allow one to infer similar, or different, underlying processes that can then be further tested. Any study that attempts to predict aberrant development from EEG, evoked potential, or slow potential data must attend precisely to the criteria measures used to determine the aberrant individual or group. The criterion measures are the weakest link in these studies. Relying on specific performance in a specific and meaningful task is presently the best tactic (unless one has data on the presence of localized brain lesions).

The Musso and Harter study (this section), which compared normal children with two groups of learning disabled children (objectively defined), demonstrates that more specific information can be obtained when more than one experimental group is included in the design. Their hypothesis that children with visual reading disabilities allocate *too much attention* to the task deserves investigation.

Developmental data exacerbate the analysis problems of ERP peak identification. Latency, polarity, and topography are features used to discriminate homologous waveform components, yet each of these parameters is subject to change with development. This problem demands close attention to behavioral measures of the process being manipulated. Variability is also an issue here. Too often, we tend to forget the variability and multiplicity of waveforms described in the literature and speak of *the* CNV, BP, or P300 waveform. It seems reasonable to expect greater waveform variation during development, especially during aberrant development. Analysis of variability could facilitate our understanding of different waveform components.

It is equally important to examine the interrelationships of changes in the development of sensory-evoked responses, CNV, readiness potential, and other aspects of ERPs in different modalities. Developmental studies can be considered another strategy to gain information on the independence (or interdependence) of these measures. With studies utilizing paradigms based in developmental theory, the promise of ERP research in relation to developmental neurobehavior theory can be realized.

There was agreement that sorting on the basis of pretrial EEG characteristics should be attempted, although this procedure may be complicated and severely reduce the number of trials. Which recording site does one use for pretrial sorting when one is interested in symmetry or topography issues? EEG amplitude and frequency predominance vary with recording site and task. Should one parcel out the underlying EEG of each site? Halliday et al. (1976) sorted on the basis of positive- or negative-going baseline and found no difference in evoked potentials. A recent study (Trimble and Potts 1975) found that alpha affected early ($<$ 120 msec) components of the visual ERP while Tanquay and Ornitz (1972) found little correlation between EP amplitude and EEG intensity in sleeping children.

These interrelationships, as well as many of the issues discussed above, require analysis epochs appropriate to the task. The developmental studies in this volume make it clear that expansion of sampling intervals is necessary if the details of children's ERPs are to be unraveled. The utility of a 500-msec poststimulus interval is severely limited (see Callaway's comments in the Psychopathology section, this volume, for counterpoint).

Developmental ERP investigators use, of necessity, a multivariate approach since they must contend with the three dimensions of stimulus, behavior, and ERP. One must maintain rigid stimulus (task) control and analyze the covariation between behavior and ERP dimensions. This triangular paradigm (Sutton 1969) is best analyzed by consideration of the variability extremes along each dimension. To tease apart ERP-behavior relationships under specific situational demands, one can sort ERP variables (e.g., CNV amplitude) along behavioral dimensions (e.g., as a function of slow vs. fast RT). The reverse procedure of sorting behavior (RT) along ERP dimensions (e.g., as a function of high vs. low CNV amplitude) provides further information on the ERP-behavior linkage. Development introduces a fourth dimension to this triangular paradigm (Karrer 1976). Behavior, physiology, and stimulus condition may be sorted along the time dimension of development. A first approximation for dealing with these complex relations is to determine the neurobehavioral relation at various levels of development.

Synopsis of Papers

Papers in this section (and other sections) provide an indication of the potential use of neuroelectric measures in the study of normal and aberrant development over the life span. At one end of the life span, Harter et al. show that visual ERP components may indicate the operation and development of two visual systems in the infant. A P130-160 component may reflect subcortical visual processes prior to 2 months of age, while a P320-400 component may reflect the development of cortical visual processes during the second month of life.

There are four papers that report ERP characteristics of reading-disabled or normal children during cognitive processing. Shelburne (Language section, this volume) examines ERPs to the third character of consonant-vowel-consonant words and nonsense syllables. He reports that reading-disabled children not only exhibit poorer discrimination of these two stimulus categories than do normal readers, but also that they fail to elicit enhanced ERPs to the third uncertainty-reducing character. Fenelon adds to the picture by showing an intriguing difference in the pattern of ERP activity between good and poor readers that seems intuitively related to language processing. Problem readers appear to generate the CNV weakly over left parietal regions. Musso and Harter report that reading-disabled children with a visual (in contrast to auditory) perceptual problem have greater differences in P300 amplitude to relevant compared to irrelevant stimuli. Reading-disabled children also had longer latencies and, perhaps, slower information processing. Friedman et al. find that children's cognitive processing affects the amplitude of components in the P300 range in a fashion similar to adults, i.e., increased P300 amplitude as a function of increased cognitive activity.

Two papers deal with multidimensional and factor analytic methodologies for determining neurobehavioral characteristics of specific clinical populations. John et al. (this volume) report their development of an ambitious neurometric battery of EEG and ERP measures that promises new power in discriminating differences in brain functioning underlying impaired (or enhanced) behavior. Laffont et al. also report a novel methodology for determining the association between clinical characteristics and neuroelectric events.

Three papers report characteristics of CNV and BP associated with motor performance and its presumed or explicit impairment. Papini et al. found that the CNV of hemiplegic children is reduced over the impaired hemisphere. Karrer et al. report that the BP waveform may change with development and take on a different waveform in aberrant populations, such as the mentally retarded. Deecke et al. show that the BP decreases in amplitude in old age and may even become a positive-going waveform. The final paper (Marsh) reviews the sparse work on ERPs during aging and suggests ERP research could be the interface between psychological and physiological research on aging.

MATURATION OF PATTERN EVOKED POTENTIALS AND VISUAL PREFERENCE IN 6- TO 45-DAY-OLD INFANTS: EFFECTS OF CHECK SIZE

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The investigation of pattern vision in normal human infants has been restricted due to the limited ability of infants to make behavioral responses to visual stimuli. Harter and White (1970) and others have shown that visual evoked potentials (VEPs) are sensitive to the sharpness and spatial frequency of patterns and that VEPs may be used to estimate refractive error and visual acuity in adults. Harter and Suitt (1970) and Harter et al. (1977b) have presented data indicating that VEPs to patterned light flashes may be used to investigate the development of pattern vision in infants during the first 6 months of life. In the present study, VEPs and the percentage time fixated (PTF) were used to estimate spatial frequency sensitivity and visual acuity in 6- to 45-day-old infants.

Method

Ten infants (seven male, three female) from an adoption agency participated in this study. Half of the infants were 6 to 26 days when tested and half were between 27 and 45 days. The experiment was conducted in the nursery with ambient lumination of about 4 mL. Infants were held by an experimenter while visual stimuli were presented 63 cm (25 in.) from the infants' eyes and subtended 22° x 22°. (See Harter et al. 1977a for a complete report of these data.)

Flashed checkerboard transparencies were used to elicit VEPs (recorded monopolarly from an active electrode placed 1 cm above the inion on the midline referenced to the right earlobe). PTF served as a behavioral measure of visual discriminability and preference. Checkerboard (individual checks subtending 11, 22, 45, 90, and 180 min of arc) and diffuse transparencies, all with equal luminance transmittance, were back illuminated with a 10-μsec flash (2.5 log units in intensity above adult threshold) every 1.1 sec. Each checkerboard was presented for 64 consecutive trials, with 4 to 6 replications of each trial series being necessary. Infants were tested every other day until sufficient data were gathered. Recordings were made only when the infant was sitting quietly and fixating.

Data were quantified by measuring VEP amplitude relative to baseline (mean amplitude during the 60- to 80-msec postflash epoch) at the following four latencies after the flash: the most positive portion between 130 and 160 msec (P2), the most negative portion between 190 and 210 msec (N2) and between 240 and 300 msec (N3), and the most positive portion between 320 and 400 msec (P4).

Results

Samples of VEPs from all infants to the diffuse and 22-min check flashes are shown in Fig. 1. Each tracing reflects an average of the four replications obtained nearest to each infant's 25th day of life.

The relationship between VEP amplitude and check size depended on the VEP component measured (Fig. 2, $p < .03$). This relationship tended to be bimodal for P2 amplitude. The 11- and 22-min checks elicited responses greater in amplitude than diffuse light or the 45-min checks ($p < .05$). The fact that P2 amplitude to the 11-min check and diffuse light differed indicates a visual acuity of 20/220 or better for these infants. A second mode was suggested by the increase in P2 amplitude ($p < .06$) as check size was further increased from 45 to 180 min.

In contrast, the effects of check size on P4 amplitude and PTF varied with age ($p < .03$). The 6- to 26-day-old infants indicated little change in P4 amplitude or PTF in response to the different check sizes. In contrast, the 27- to 45-day-olds showed a linear increase in P4 amplitude and PTF as check size was varied from diffuse light to the largest check (180 min). The correlation between P4 amplitude and PTF was highly significant ($r = 0.92$, $p < .01$). Regression lines were best-fit to these measures and indicate extrapolated visual acuities (arrows in Fig. 2) of 6 and 10 min, respectively. These values are reasonably similar and correspond to acuities of 20/120 and 20/200, respectively.

Discussion

What optical or neural factors might underlie the shape of the function between VEP amplitude and check size and the changes in this function during the first 2 months of life? A review of optical changes during the first 2 months (Maurer 1975) indicated that such changes may not account for the present results. Maurer's review and others, in conjunction with the finding that age selectively influenced the later VEP components, suggest the effects of age may be attributed to neural changes.

The two types of functions between VEP amplitude and check size, the first being reflected by P2 amplitude in response to small check sizes and the second by P4 amplitude in response to larger check sizes, suggest one interpretation. Inverted U-shaped functions, associated with changes in spatial frequency, appear to reflect the receptive field and spatial tuning characteristics of the neurons activated. This interpretation has been applied to psychophysical data (Blakemore and Campbell 1969), human EP data (Harter and

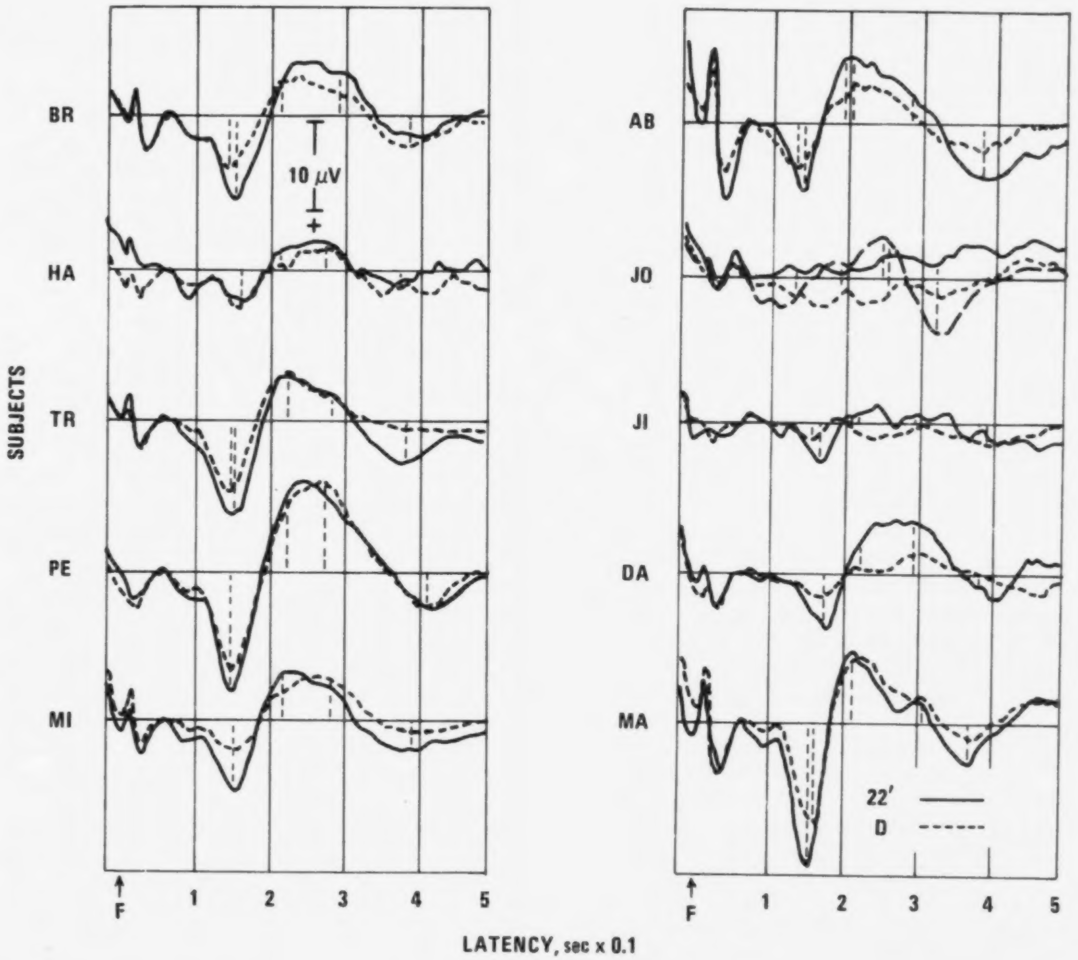

Fig. 1: Visual evoked potentials to the 22-min check size and diffuse flash (D) from each infant that participated in the experiment. Each tracing is an average of 128 potentials obtained nearest to each infant's 25th day of life. The extra dashed VEP for JO was in response to the 180-min checkerboard. The vertical dashed lines indicate latencies where P2, N2, N3, and P4 amplitude measures were made.

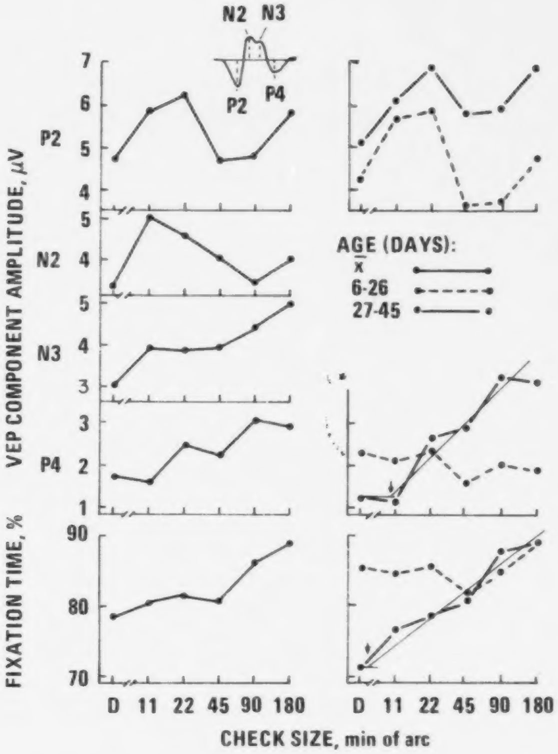

Fig. 2. Effects of the size of checks in checkerboard flashes and of diffuse flashes (D) on the amplitude of the four VEP components (first four rows) and the percentage time fixated (bottom row). Solid lines indicate the means based on all subjects (left column), dashed lines indicate the means of data collected from 6 to 26 and 27 to 45 days after birth (right column). Regression lines were best-fit to P4 amplitude and the percentage time fixated in the 27- to 45-day-old group; the X-axis intercepts (vertical arrows) begin at 10 and 6 min. respectively.

White 1970, Harter 1970, Armington et al. 1971, Karmel et al. 1974, Karmel and Maisel 1975), and animal single-unit data (Campbell et al. 1969). If this interpretation is applied to the present data, it suggests that at least two aggregates of neurons contributed to the effects of check size on VEP amplitude, one primarily reflected by the early VEP components and tuned to relatively high spatial frequencies and the other by the late VEP components and tuned to relatively low spatial frequencies.

Reviews of behavioral, physiological, and anatomical data related to infant development (Bronson 1974, Cohen and Salapatek 1975) also suggest that two neural systems differentially contribute to visual capacities manifested in the first 2 months of life, one subcortical and the other cortical. Subcortical mechanisms may account for visual capacities manifested in the first month, whereas cortical mechanisms may account for the abilities that become manifest starting in the second month.

A number of factors suggest that the bimodal nature of the present data may be interpreted within the framework of subcortical and cortical mechanisms. The first mode was primarily due to changes in P2 amplitude, a relatively early component of the VEP and more coincident in time with the arrival of subcortical activity at the cortex. The early component was sensitive to small check sizes (higher spatial frequencies) as are the subcortical (geniculate) neurons of animals (Campbell et al. 1969) and were poorly correlated with the behavioral PTF measure. In contrast, the second mode was primarily due to changes in P4 amplitude, a later component of the VEP and more likely to reflect the processing of information within the cortex. The late component was most sensitive to larger check sizes (lower spatial frequencies) as are cortical, particularly complex, neurons (above studies). P4 amplitudes were highly correlated with the behavioral PTF measure, and were not influenced by check size until the second month of age. The above indirect line of evidence suggests that the spatial frequency sensitivity of the early VEP components may reflect the contribution of subcortical mechanisms and the late VEP components may reflect the contribution of cortical mechanisms. If this interpretation is correct, the change in responsivity of the late VEP components and the transition from passive to more active and discriminating visual preference indicate an acceleration of cortical function between 28 and 45 days after birth.

CONTINGENT NEGATIVE VARIATION, EVOKED POTENTIAL, AND PSYCHOPHYSICAL MEASURES OF SELECTIVE ATTENTION IN CHILDREN WITH LEARNING DISABILITIES[1]

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This investigation was conducted to specify some of the electrocortical correlates of learning disabilities in children. A reading disability may be defined as "the failure to learn to read with normal proficiency despite conventional instruction, a culturally adequate home, proper motivation, intact senses, normal intelligence, and freedom from gross neurological effects" (Eisenberg 1964, p. 65). A problem in assessing the etiology behind learning disabilities is that the contribution of specific component skills that characterize the disability has not been identified. Learning disabilities have been attributed to a number of interrelated processes–e.g., perceptual and psycho-motor (Wold 1969), neurological (Ingram 1971), and attentional (Anderson et al. 1973). Attentional effects on electrocortical activity and performance in reading disabled and normal children were compared in this study with the aid of the visual evoked cortical potential (VEP), contingent negative variation (CNV), and reaction time (RT).

Method

Twenty-seven children, divided into three equal groups matched for age (7 to 12), IQ (above 90), and sex, participated. One group consisted of children classified as normal (N) in reading ability and the other two groups consisted of children classified as having reading disabilities attributed respectively to visual (VRD) and auditory (ARD) perceptual problems. Classifications were made on the basis of the Slingerland Screening Test for Identifying Children with Specific Language Disabilities. All children were free from gross neurological damage and physical disabilities, according to medical records, and were taking no form of medication. The children were solicited through the Guilford County School System. Visual acuity, vertical and lateral phorias, and color blindness were evaluated by subjective reports in conjunction with an Ortho-Rator and Ishihara color plates. Spherical refractive error was assessed by both VEPs (Harter and White 1968) and subjective report. The frequency of detected visual anomalies did not differ significantly between the three groups.

The subjects' abilities were assessed in a visual discrimination attentional task that consisted of flashing a warning stimulus, S1 (a clown's face), followed after 1100 msec by one of two randomly presented flashes, a relevant (S2rel) or an irrelevant (S2irrel) stimulus. The entire S1-S2 sequence was repeated once every 5 sec. The subject was required to lift his finger off a microswitch key within a critical period of time. If the subject responded to S2rel within this period (Hit) or withheld a response to S2irrel (Correct Rejection), he was given a token; if he responded to S2rel late (Miss) or to S2irrel (False Alarm), he lost a token and was given immediate negative feedback in the form of a loud click. The click was given 1000 msec after S2 in the case of a Miss and at the time of response (mean latency of 395 msec after S2) in the case of a False Alarm. Any auditory evoked potentials to these clicks were sufficiently after S2 to ensure they would not contaminate the VEP measures employed. Tokens were exchanged for rewards after each experimental session. The False Alarm and Hit rates were used as a behavioral measure of attention or discriminability (d′) according to Signal Detection Theory (Swetts 1964). It may be noted that the critical period of time for the purpose of feedback was the median RT for the problem and subject (as determined from previous data) whereas for the purpose of determining d′, it was 1000 msec. The response accuracy measure, therefore, was independent of response speed.

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[1] These data are portions of M. F. Musso's dissertation, "Psychophysical Performance, Contingent Negative Variations, Visually Evoked Cortical Potentials, and Selective Attention: a Behavioral and Neurophysiological Assessment of Learning Disabilities in Children," conducted in the Department of Psychology, University of North Carolina at Greensboro, 1975.

Four pairs of S2s were presented, each representing a different level of complexity in terms of discriminability: red and green diffuse light; vertical and horizontal lines; the letters *b* and *d*; and the words *was* and *saw*. Each stimulus of the pair was both relevant and irrelevant for one condition, giving a total of eight different problems, two for each pair. Each condition consisted of at least 32 presentations of each stimulus of a pair in random order. The eight problems were presented to each subject twice, each pair being presented four times (replications). Stimuli were presented on a LVE Model 1346 Multiple Stimulus Projector and were 40 msec in duration and 2.5 degrees in subtense.

Cortical potentials were recorded, amplified, and averaged starting at the onset of S1. Active electrodes were placed approximately over Oz and Cz and referenced to the right earlobe. The one-half amplitude low and high frequency filters of the amplifiers were set at 0.15 and 35.00 Hz. A signal averaging computer was programmed to average activity during the entire S1 to S2 interval and to sort the 32 presentations of S2 relevant and irrelevant. Therefore, CNVs prior to S2 and VEPs following S2 were recorded and averaged. CNVs were quantified by measuring the area under the CNV deflection in terms of a voltage-time dimension (Tecce 1972). VEP latency was quantified by measuring the time between onset of S2 and the peak of the prominent positive component occurring between 270 and 435 msec (P300) after onset of S2. The effect of selective attention to relevant and irrelevant stimuli on VEP amplitude was quantified by measuring the peak-to-trough amplitude of the surface negative and positive components at about 200 and 300 msec, respectively, after S2 and finding the difference in this measure when a given S2 was relevant or irrelevant.

Results and discussion

The problem type differentially influenced d′, CNVs, and VEPs. Color and line orientation discriminations yielded higher d′ scores ($p < .01$) than letter or word discriminations (Fig. 1). The largest Oz VEP difference between relevant and irrelevant stimuli (Fig. 1) was also observed for colors ($p < .05$). VEP and d′ results indicate that colors were discriminated more readily than words. Smaller CNVs (Oz and Cz) were obtained to color than word stimuli ($p < .05$) (Fig. 2), which indicated a greater state of preparedness or arousal for the word problems. Together, these measures show that the word problems were more difficult and arousing to the children.

The relevancy of stimuli had a pronounced effect on VEP amplitude: all children gave larger VEPs to a stimulus when it was relevant as compared to irrelevant. The VRD group showed greater relevant-irrelevant differentiation in their Oz VEPs than the N group ($p < .05$) (Fig. 3). This greater differentiation in the VRD group suggests that they were selectively attending more than the other groups. As the children

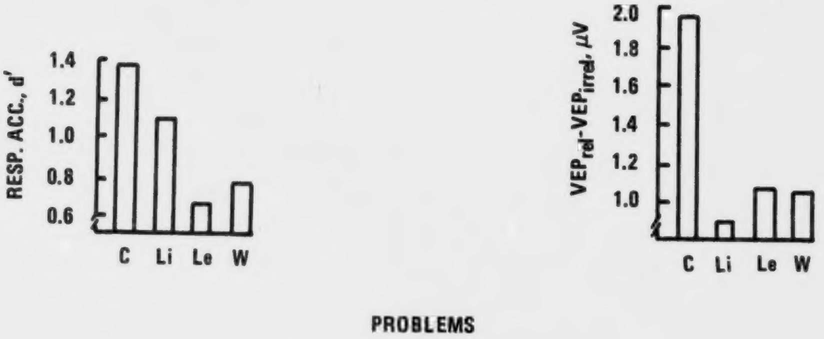

Fig. 1. Effect of problem type on behavioral response accuracy (d′) and VEP measures of selective attention [*colors (C), line orientation (Li), letters (Le), and words (W)*].

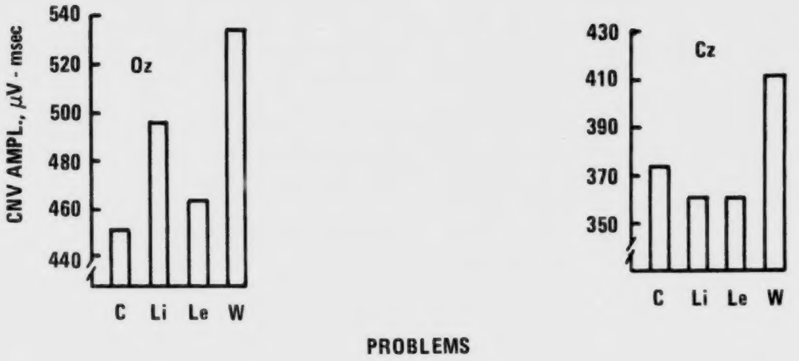

Fig. 2. Effect of problem type on CNV amplitude. Same abbreviations as Fig. 1.

in the three groups were all trained to the same level of performance on the visual discrimination tasks, it appears that the VRD group compensated for their deficiency by greater selective attention in the visual discrimination task.

The latency of the P300 component of VEPs recorded from both the vertex and occiput indicated that VRD children had longer latencies than ARD children, who, in turn, had longer latencies than N children ($p < .05$) (Fig. 4). These latency differences were interpreted as suggesting that the reading disabled child processes sensory information at a slower rate than the normal child, which may be indicative of a neural deficiency.

The VEP measures of component latency and selective attention to relevant and irrelevant stimuli, which yielded significant group differences, support the notion of a sensory-specific deficit in the reading disability syndrome. The separation of reading disabled children according to modality-specific perceptual capabilities is amenable to the present study's findings.

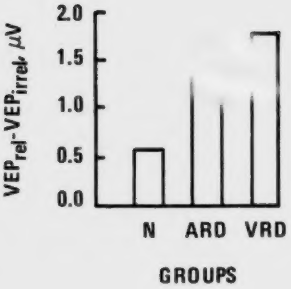

Fig. 3. Difference in VEP amplitude due to selective attention in the normal (N), auditory (ARD), and visual reading disability (VRD) groups.

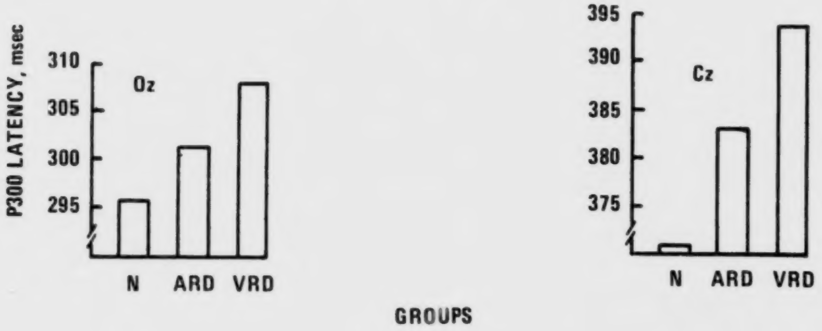

Fig. 4. Mean latencies of the P300 component in the normal (N), auditory (ARD), and visual reading disability (VRD) groups.

HEMISPHERIC EFFECTS OF STIMULUS SEQUENCE AND SIDE OF STIMULATION ON SLOW POTENTIALS IN CHILDREN WITH READING PROBLEMS[1]

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It has generally been accepted that CNV amplitude is independent of the modality of stimuli employed. The assertion was originally made by Walter (1967), but formal experimental tests were not carried out until recently, presumably because experimenters, in manipulating stimulus mode, obtained generally confirmative results. Supportive experimental evidence was put forward by Blowers et al. (1976) who, using nine combinations of auditory, tactile, and visual stimuli and measuring vertex CNV, found no modality-related differences.

There have been opposing findings. Gaillard and Naatanen (1976) reported modality-related differences in CNV measured from three scalp sites (vertex, mid-left temporal, right occipital). They drew attention to the differences in effects at different sites, in different parts of the waveform, and for the warning and imperative stimuli.

The question of CNV asymmetry is also of great interest in relation to clinical problems, such as localising the motor speech area (Low et al. 1976) or throwing light on the brain responses of stutterers (Zimmerman and Knott 1974). It is of special importance in assessing cerebral dominance and hemispheric lateralization of problem readers.

Earlier studies of CNV features of dyslexic children suggested that the nature of S2 has a determining effect on electrical activity that develops before and after S2 (Cohen et al. 1965, Fenelon 1968). Reading, particularly in interaction with a tutor, involves the rapid sequencing of visual and auditory identifications of words, or elements of words. Alternatively, a particular sound constellation is required to be matched by a visual identification. In physical elements, the child is experiencing a sequence of stimulation that is visual-auditory (V1-A2) or auditory-visual (A1-V2). These sequences are fundamental to certain techniques of teaching. In most instances, the visual performance involves eye fixations followed by saccadic movements to fixate a visual feature appearing in the right hemifield.

The aim of the present experiment was to examine the effects of lateralised stimulation on certain measures of the event-related slow potential (SP), comparing reading problem children with normal readers in unimodal and bimodal stimulus sequences. On the basis of previous neuropsychological studies (to be reported), it was hypothesised (1) that the problem readers would develop CNV comparatively weakly in the left parietal region and (2) that right hemisphere responses would be more highly correlated in the problem group than in the normal group.

Method

Subjects

Seven problem readers, mean age 114 (± 11.6) months, mean IQ 113.4 (± 12.8), were referred by a special class supervisor as being retarded 12 months or more in reading achievement on at least two out of three group reading tests (Australian Council for Educational Research, Melbourne) and on the Schonell R1 word recognition test. The mean reading age of the problem readers was 92 (± 7.2) months compared with 118 (± 5.4) months in the normal readers group. The seven normal readers were of comparable chronological age (114 ± 5.4 months) and intelligence (mean IQ 117 ± 13.4).

The handedness of the subjects, assessed by several different methods, was uniformly righthanded. Although hand of response has been shown to affect SP symmetry (Otto and Leifer 1973, Kutas and Donchin 1974), response laterality was not used as an

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[1] Computer programs used in this study were provided by the Burden Neurological Institute, Bristol, England. The author wishes to thank Mrs. S. Byron for typing the manuscript.

independent variable because of time limitations in the full experimental sequence.

Apparatus

A Devices M-19 unit was interfaced with a remotely located PDP-12 computer. Low band-pass filters were set at 15 Hz, and time constant at 3 sec. Ag/AgCl electrodes were applied to the scalp at sites iF4, iF3, iP4, and iP3 and were referred to common mastoids. The bipolar vertical EOG was also recorded. Audio signals were 700-Hz or 1000-Hz pure tones, duration 100 msec, delivered through earphones at 70 dB. Visual signals were low-intensity flash stimuli subtending a retinal angle of 1° and displaced approximately 9° from a central unilluminated fixation spot that was also employed for eye fixation when auditory stimuli were presented. Visual trials were conducted in semidarkness in a sound-attenuated room.

Procedure

The paradigm employed was the simple S1-S2 motor response sequence (ISI 1400 msec and ITI greater than 10 sec). The subject responded to S2 with a button held in the right hand. The parent and an assistant remained in the room to keep up motivation and alertness and to provide company for the child.

Following training trials, the experiment was conducted in two stages: (1) On-line averaging of eight eye-movement-free responses in each of the following four conditions (where A1 = 700-Hz tone; A2 = 1000-Hz tone; V = visual stimulus; L = left ear or left visual field; R = right side):

LV1 - LV2, RV1 - RV2, LA1 - LA2, RA1 - RA2

Sequencing of conditions was varied from subject to subject to avoid systematic arousal effects. During averaging runs, the subject was advised of his reaction time following each trial and encouraged to improve his performance. (2) Each subject received 16 trials each for A1 - RV2 and RV1 - A2 (A = binaural 1000-Hz stimulation) in predetermined random sequences. Acceptable single trials were stored for off-line processing. At this stage, the instructions informed the subject that the S1 modality predicted the other-modality stimulus at S2.

Various SP measures were taken using off-line cursor and integration programs. The analyses reported below were conducted on maximum peak-to-peak CNV amplitudes measured during the interval from 400 msec post-S1 to the onset of S2. Maximum positive peak was determined for the unimodal sequences in the interval 400 to 480 msec post-S1. In the bimodal sequences, post-S1 positivity was prolonged and the corresponding point was taken in the 650- to 730-msec interval. Maximum negative peak in both sequences was measured in the 80-msec interval prior to S2. The stimulation sequence and measurement interval (unimodal condition) are illustrated in Fig. 1.

Results

Sample CNV waveforms (auditory unimodal condition) are illustrated in Fig. 1. Means and standard deviations for the unimodal conditions are represented graphically in Fig. 2. Mean maximum CNV and standard deviation in the bimodal stimulation conditions are shown in Table 1.

Data from unimodal and bimodal conditions were submitted to 2 (groups) x 2 (stimulus conditions) x 2 (hemispheres) x 2 (anterior-posterior locations) analyses of variance with repeated measures on factors 2 to 4. Factors with $p < .10$ are grouped in Table 2.

To assess intra- and interhemispheric symmetry of waveforms, correlation coefficients were computed from group-average data for each waveform pair. Correlations were computed for each waveform pair by shifting in one-point increments ±64 points from the origin. The maximum correlation observed for each pair is shown in Table 3 for each unimodal stimulation condition and group. (This analysis was not undertaken for bimodal stimulation data.) Maxima occurred at or near zero displacement. Correlations coefficients $r \geqslant 0.26$, $t(62) = 1.98$ are significantly different from zero. Correlation coefficients were Z-transformed and differences between pairs of coefficients were tested for significance in relation to the standard error (SE_Z) = 0.18.

Significant differences between pairs of coefficients in a row or in a column are indicated in Table 3. Between-group differences for right hemisphere associations support the hypothesis that right hemisphere responses would be more highly correlated in the problem group than in the normal group. Some correlations support differential hemispheric organization of responses in problem and normal readers.

Discussion

The data for unimodal visual stimulation and for bimodal stimulation do not support the hypothesis that CNV develops comparatively weakly in the left parietal region of problem readers. Some support, however, is derived from the auditory stimulation data if one is willing to accept trends ($p < .10$) obtained on a stringent analysis applied to the data from small groups of problem readers who were not extreme cases of disability. The first-order interaction for groups x location reflects the strong development of parietal CNV in the normal group. The higher order interactions ($p < .10$) result from complex differences

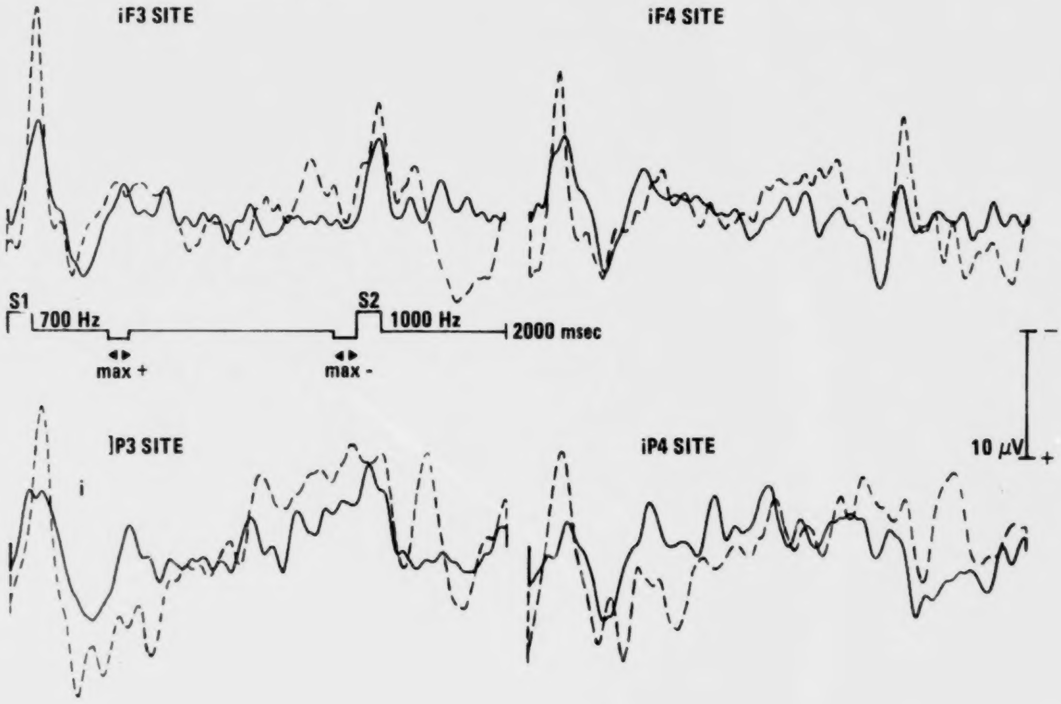

Fig. 1. Group average CNV. Auditory S1-S2 sequence to right ear. Problem readers, heavy trace. Negative up.

Table 1. Group Mean (M) CNV Maximum Amplitude and Standard Deviation (SD), in Microvolts, for Bimodal Condition

Stimulation condition[a]	Experimental group	Recording sites							
		iF3		iF4		iP3		iP4	
		M	SD	M	SD	M	SD	M	SD
A_1 - RVF_2	Problem	11.7	5.37	15.1	5.26	20.3	7.76	19.7	5.93
	Normal	22.5	6.19	19.9	4.93	26.6	12.27	25.9	8.35
RVF_1 - A_2	Problem	17.9	6.31	14.5	3.93	21.1	10.74	22.9	4.96
	Normal	19.9	4.62	21.5	6.22	32.2	11.03	34.3	8.39

[a] RVF = right visual field; A = both ears.

between groups in parietal CNV amplitudes when the right ear receives the signal. In absolute amplitude, the left parietal CNV of problem readers is only 55 percent of that for the normal group in both auditory stimulation conditions. Right parietal CNV of problem readers actually exceeds that of the normal group when the left ear receives the signal. Over all six stimulation conditions, the problem group averages 63 percent of normal group CNV amplitude at the left parietal site, while at the right parietal site the figure is 81 percent. This indicates a relative left-sided weakness, in accordance with the first hypothesis.

From Fig. 2, a difference in response between groups is observable for left- and right-sided auditory stimulation. At the left parietal site, CNV amplitude in

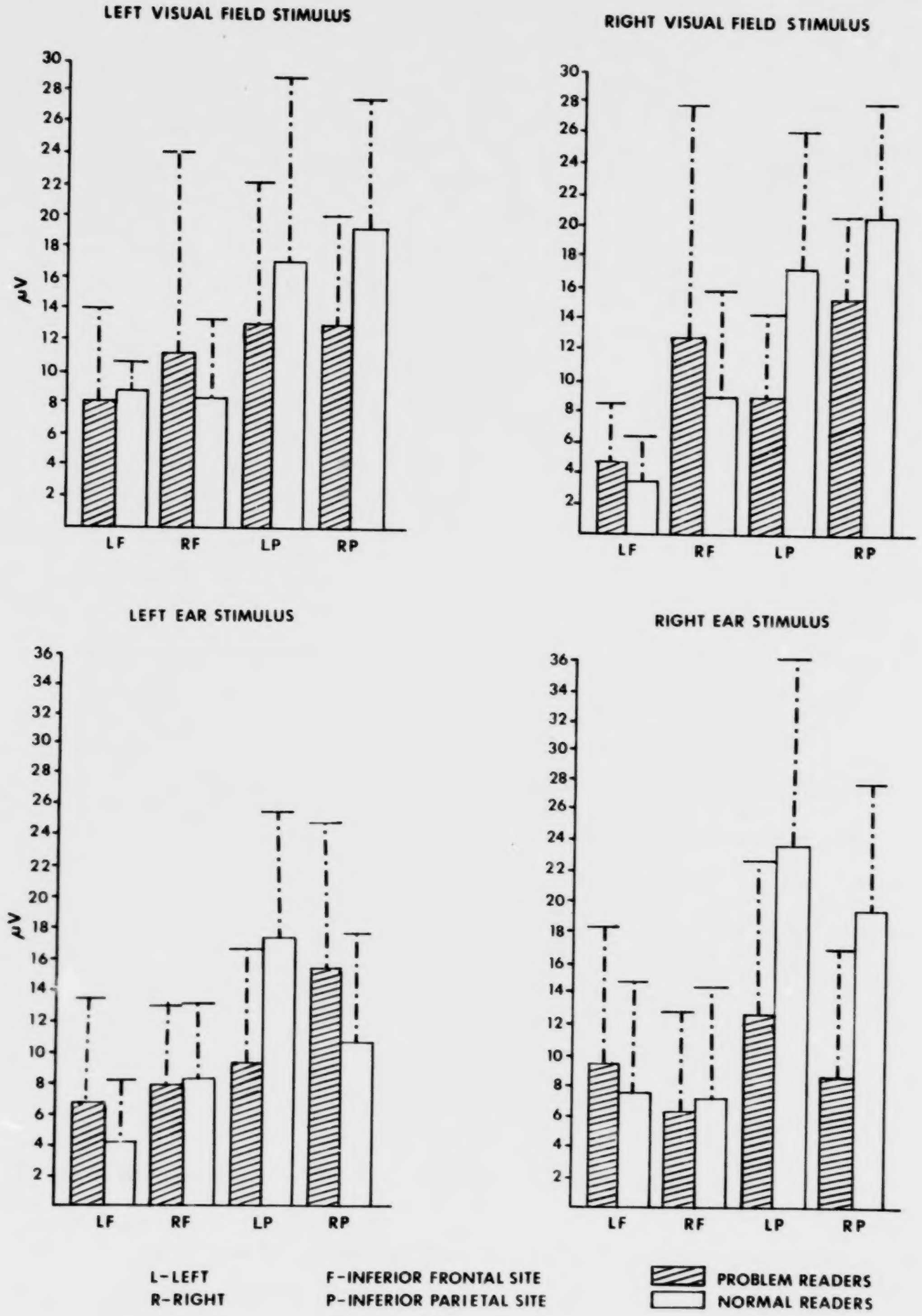

Fig. 2. Mean maximum positive to negative amplitude (microvolts) in CNV period between 400 to 490 msec and 1310 to 1400 msec post-S1.

Table 2. ANOVA Summary of CNV Measures (df = 1/2 All Factors)

	Stimulus conditions					
	Unimodal				Bimodal	
	Visual		Auditory			
	F	p	F	p	F	p
Groups					10.82	.01
Hemispheres	5.38	.05				
Location	8.96	.05	20.22	.001	29.48	.001
G x L			4.24	.10		
G x S X L			4.57	.10		
G x H x L			3.40	.10		

both groups is more than 30 percent greater for right-sided stimulation. At the right parietal site, the problem group loses 45 percent amplitude compared with an increase of more than 80 percent in the normal group.

Other features of interest are: (1) The problem group CNV amplitude is generally less than that of the normal group, the difference being significant (p ‹ .01) under bimodal stimulation (Table 1). (2) Frontal CNV amplitudes in the problem group exceed those of the normal group for unimodal visual stimulation (Fig. 2). The differential tends to disappear when auditory stimulation is used (Fig. 2) and is reversed under the more complex bimodal stimulation conditions (Table 1). (3) Parietal CNV amplitude greatly exceeds that for frontal CNV in both groups, as shown by the significant locations main effect across all stimulus conditions (Table 2).

The second hypothesis receives partial support from the correlations. Right hemisphere responses are more highly correlated in the problem group than in the normal group, but only in the visual stimulation conditions.

In CNV studies, the association between physical stimuli confers symbolic meaning on the simple stimulation sequence. Even in the absence of instructions that give specific meaning to S1 and S2, the conditional linkage between the two stimuli evokes some level of language mediation of the contingency involved, leading to the initiation of the required motor response. The electrophysiology of cerebral response to this simple configuration may provide clues to the topography and dynamics of language processing and production in the brain of problem learners and retarded persons (Karrer and Ivins 1976c) as well as normals. The present data raise a number of questions concerning the organization of electrical activity to

Table 3. Intra- and Interhemispheric Correlation Maxima of Waveform Pairs in Unimodal Stimulation Conditions[a]

			Sites intercorrelated					
			Interhemispheric			Intrahemispheric		
Modality	Field	Group	iF3 - iF4		iP3 - iP4	iF3 - iP3		iF4 - iP4
Visual	Left	Problem	.20	**	.87	.09	**	47 *
		Normal	.73		.83	.08		.20
	Right	Problem	.50	**	.87	.20	**	.57
		Normal	.74		.86	.36		[b] .29
Auditory	Left	Problem	.71		.64	.55 *		.61
		Normal	.76		.68	.25	**	.67
	Right	Problem	.63 *		.47 *	.63	*	.29
		Normal	.78	*	.89	.49		.38

[a] If $r > 0.26$, $p < .05$. The difference between adjacent pairs of coefficients in rows and columns was also evaluated (see text) and significant differences are indicated by asterisk(s).

[b] Trend: $p < .10$.

*diff: $p < .05$.

**diff: $p < .01$.

lateralized auditory stimulation. Intrahemispheric correlations show an interesting difference in pattern between groups. In the right hemisphere during right-sided stimulation, frontal-parietal correlations are lower in problem readers than in normals. Conversely, in the left hemisphere during left-sided stimulation, frontal-parietal correlations are lower in normals than problem readers. Also the cross-hemisphere correlations (especially parietal) are strikingly different between the groups when stimulation is right-sided.

In view of the small sample and limited range of reading disabilities in the present study, it is prudent to withhold attempts at explanation until more data are available.

Summary

SPs were recorded from inferior frontal and parietal sites over both hemispheres of problem and normal readers of equal age, schooling, and intelligence. Stimulation was given in visual, auditory, and mixed modality sequences. Correlations between SPs in the right hemisphere were relatively high in the problem group, but differences between groups were not observed in auditory conditions. The results support the hypothesis that problem readers generate CNV relatively weakly in the left parietal region.

TASK-RELATED CORTICAL POTENTIALS IN CHILDREN IN TWO KINDS OF VIGILANCE TASKS

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The existence of long-latency positive waves recordable from the scalp of adult subjects, generally referred to as Association Cortex Potentials (Ritter et al. 1972) or P300 (Sutton 1969), has been known for over a decade. These late positive waves have been little studied in children. With renewed interest in the neurophysiologic bases of childhood learning disorders and in neurophysiologic development in general, data have been published recently on "task-related" cortical potentials in 6- to 8-year-old children (Kurtzberg et al., in press); "event-related" slow potentials in aphasic, dyslexic and normal children (Otto et al. 1976); visual event-related potential correlates of informational linguistic content in normal children (Shelburne 1973); and visual event-related potential correlates of meaningful stimuli in normal children (Symmes and Eisengart 1971).

Kurtzberg et al. (in press) presented data showing the existence of late positive component morphology similar to that of the adult by the age of 8. Shelburne (1973) replicated in children his earlier study with adults (Shelburne 1972), showing an enhanced late positivity to a third consonant, which delivered task-relevant information. Symmes and Eisengart (1971) reported a late vertex negative wave, peaking at about 500 msec, to meaningful visual stimuli. Other investigators have also reported the occurrence of late negative deflections to complex visual patterns in children (Kurtzberg et al., in press; Neville 1975), as well as in adults (Cohen and Walter 1966, Courchesne et al. 1975, Lifschitz 1966). No general hypothesis as to what this negative wave represents has been formulated.

The present study is concerned with initial analyses of late positive waves recorded in response to numeric stimuli while children were involved in information processing in two different vigilance tasks. In one task, the subject had to respond to the same target throughout a block of trials, while in the other, the subject had to respond to the repetition of any immediately preceding stimulus. The processing demands of the latter task were greater, since the subject had to hold the stimulus in memory and wait to see if it would repeat.

These children formed part of a normal control group used to study a large number of biological, sociological, and psychological variables in a longitudinal project concerned with children at high risk for schizophrenia (Erlenmeyer-Kimling 1971, 1975). The data from the high risk sample and from additional control children will be discussed in a subsequent report. Data from an earlier version of one of the tasks have been reported elsewhere (Rutschmann et al. 1977).

Method

Six children, aged 11-14, served as subjects. This project was their second round of testing, occurring approximately 2 years after they were initially seen. Each child received a psychophysiologic battery, which took approximately 2.5 hours and included Tasks A and B. Task A was a vigilance task (Orzack and Kornetsky 1966 standard task) in which the signal was the number 08 (15 per block of 60 stimuli) and the nonsignals were 15 of numbers from 02-19, each occurring 3 times during a block. Thus, the signal to nonsignal ratio was 1:4. Task B (similar to the Orzack and Kornetsky 1966 A-X task), which always followed Task A, was a vigilance task with different demands. The signal in Task B was the repetition of any immediately preceding number (which occurred 16 times per block), and the nonsignals were 12 of the numbers from 02-19, occurring 4 times each within a block (48 per block). This procedure yielded a signal to nonsignal ratio of 1:4. Any bias that may have been introduced by the fact that Task B always followed Task A is opposite to the hypothesis, since the prediction was that late positive component amplitude would be larger to nonsignals in Task B (i.e., opposite to habituation effects). In both tasks the required response was a brisk extension of the right wrist. Reaction time was measured at the onset of the EMG burst.

For each task, a practice block of trials was given before each set of seven to eight blocks to ensure that the subject was responding correctly and was producing usable EMG pulses (due to equipment malfunction, two subjects received only 7 blocks of each task). A short rest between blocks and a 5 to 10 min rest between tasks were given. Stimuli (50-msec duration) were presented on a slave scope, transmitted to a video monitor in the subject's room by a video camera, and were flashed at moderate intensity at a visual angle of 2 deg 20 min. The ISI was 1.5 sec. EEG was recorded from Fz, Cz, Pz, and Oz, referred to the right ear; and vertical EOG was recorded from an electrode located above the right eye. Physiologic signals were recorded by means of Ag/AgC1 electrodes and were amplified with a time-constant of 1 sec and a gain of approximately 20,000. Data acquisition and stimulus presentation were under control of a PDP 11/10 computer. Data were digitized at 4-msec intervals for a total of 1100 msec (100 pre- and 1000 post-stimulus) and were stored on 9-track digital tape for off-line analyses. Ideally, there were 120 signals and 360 nonsignals for Task A and 128 signals and 384 nonsignals for Task B. Because of blinking and eye movement artifact, however, roughly one-quarter to one-half the trials for a given subject had to be eliminated to produce an artifact-free average. Great care was taken to eliminate these artifacts due to their known effect on event-related potentials, especially in children (Eisengart and Symmes 1971, Shelburne 1973).

Results

Fig. 1 presents the grand mean waveforms for the six subjects for each type of stimulus from each task. The occipital visual event-related potential consisted of three initial peaks, P143, N187, and P231, which remained essentially constant in amplitude and peak latency in all conditions. Grand mean waveforms revealed several additional peaks, each of which possessed a characteristic timing and topography and varied to differing degrees across conditions. In order of increasing latency, the principal positive peaks can be identified as follows:

1. P176 identified solely in the parietal placement in all conditions.

2. P220 most clearly defined in frontal and central placements of nonsignal averages.

3. P264 present in the signal averages of both tasks in the frontal and central recordings.

4. P319-352 of greatest amplitude in the parietal region, but also present in the central and occipital areas, and larger to signal than to nonsignal stimuli.

5. P462-484 largest at the parietal placement, identifiable in all loci, and larger for signal than nonsignal stimuli. This late positive activity returned slowly to baseline in the parietal and central areas.

A late negative wave, peaking at about 600 msec, was seen only in response to signals and was more negative in Task A than in Task B.

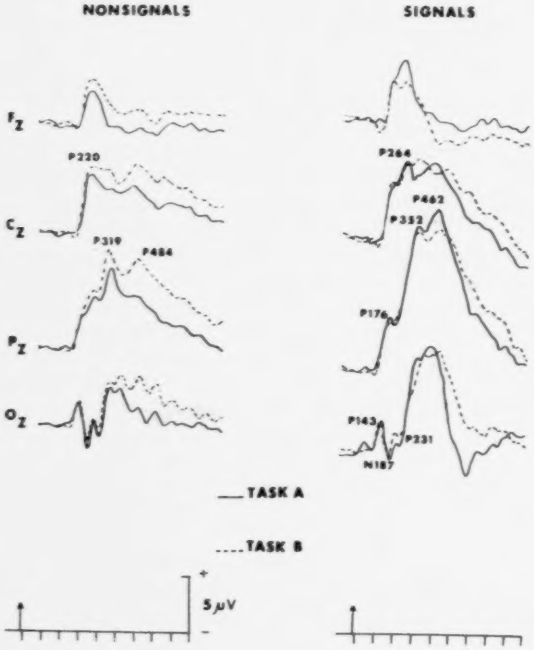

Fig. 1. Grand mean event-related potentials across six subjects. Stimulus onset at 100 msec. Time lines every 110 msec.

Using the grand mean waveforms as a template, two of the investigators (DF and HV) independently determined the presence or absence of these late positive components in the data of individual subjects. A component was considered present only if it had a clearly defined peak at a given electrode and if its topography and latency were similar to that of the grand mean. Amplitude of a given component was scored by first determining the electrode at which it was most clearly defined and then measuring amplitude at that latency at each of the other electrode sites. Thus, although P200-264 was present as a well-defined peak mainly at the frontal and central electrodes, an amplitude gradient across electrodes was obtained by means of this method.

Table 1 presents (1) mean latencies, as measured in the data of the individual subjects, for each of the peaks (labeled for their latencies, taken from the grand mean waveforms) and (2) the number of subjects in whom the investigators scored a given peak as present. T-tests for correlated means revealed no significant latency differences between tasks for any of the components.

Fig. 2 presents the mean baseline-to-peak topographical distribution for these four positive peaks. Unconnected points represent P143 of the visual evoked potential. T-tests for correlated means showed no significant amplitude differences in P143 between tasks for either signals or nonsignals.

Analyses of variance for repeated measures (task and electrode location) were used to assess significance. With the exception of P176 to signals, electrode location was a significant source of variation for all components to both signals and nonsignals ($p < .05$ for P176 to nonsignals; $p < .001$ for all others). P176 amplitude was larger to Task B nonsignals than to Task A nonsignals [$F\ (1,5) = 9.8$, $p < .05$]. For P220-264, no significant task effects were observed for either signals or nonsignals. For P319-352, and only for nonsignals, Task B produced larger amplitudes than Task A [$F\ (1,5) = 4.8$, $p < .07$]. For P462-484, and again only for nonsignals, Task B produced larger amplitudes than Task A [$F\ (1,5) = 4.8$, $p < .07$]. The only significant task effect for signal responses was for P462-484, where the task x electrode location interaction was significant [$F\ (3,15) = 5.4$, $p < .01$]. Tests for simple effects (Winer 1962) showed that this interaction was due to greater amplitudes at Fz and Pz during Task A than Task B ($p < .01$ at both), while there was no difference at Cz or Oz. This finding is possibly due to longer and more variable reaction times in Task B than in Task A. This factor would lead to increased late-component jitter in Task B relative to Task A and, thus, a decrease in amplitude. It is also possible that decreased temporal overlap of these late components in Task B, relative to Task A, contributed to this effect.

The results demonstrate an effect of processing complexity on late positive component amplitude elicited by nonsignals of Task B. This electrophysiologic effect was paralleled by behavioral changes in that mean reaction time was longer in Task B (544 msec) than in Task A (466 msec).

Discussion

These data show an effect of cognitive processing demands on late positive component amplitude and replicate the findings for adults (Friedman et al., this volume). As in our interpretation of the adult data, the most parsimonious explanation of the children's data is that late component amplitude to nonsignals in Task B is increased, relative to those in Task A, because of more complex processing demands for the nonsignal

Table 1. Mean Peak Latencies, Standard Deviations (SD), and Number of Subjects (N) Showing Each Component

	Nonsignals								Signals							
	Task A				Task B				Task A				Task B			
	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz	Fz	Cz	Pz	Oz
P176																
Mean	183	185	185		191	192	189		185	189	187		194	194	194	
SD	19	20	19		17	17	19		23	21	24		19	19	19	
N	4	3	5	0	4	2	4	0	6	6	6	0	6	6	6	
P220-264																
Mean	240	244			246	248			273	273			284	286		
SD	27	29			16	29			14	24			14	11		
N	6	6	1	1	5	5	1	1	5	5	1	1	5	4	0	0
P319-352																
Mean	347	347	347	343	352	352	350	356	365	365	363	370	357	359	359	363
SD	31	31	31	27	30	28	29	37	33	34	33	33	28	25	25	32
N	2	2	5	6	3	4	6	5	3	3	6	6	3	3	6	6
P462-484																
Mean	491	491	488	490	515	512	510	508	482	471	473	471	480	482	482	480
SD	29	28	29	30	38	38	29	32	44	35	36	34	28	28	32	41
N	4	4	4	2	6	6	6	3	4	5	5	6	2	2	4	5

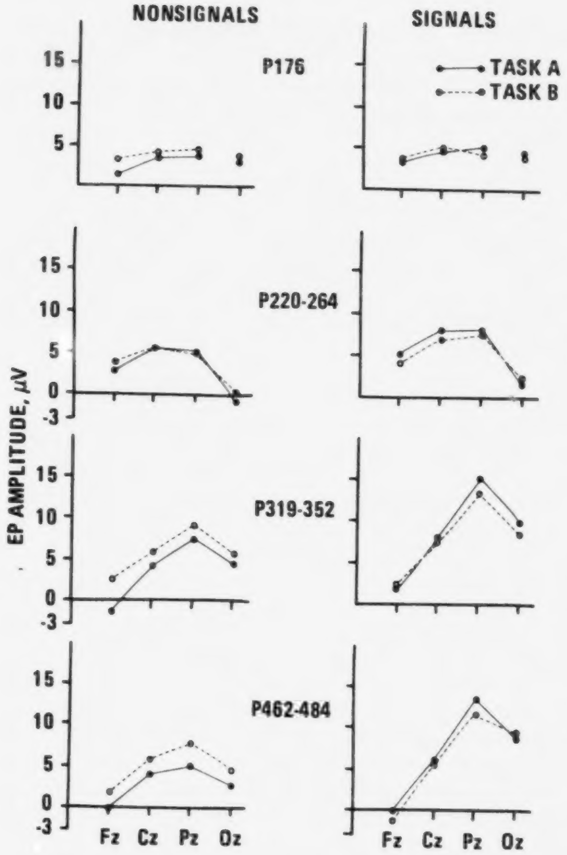

Fig. 2. Mean baseline-to-peak signal and nonsignal amplitudes for the four positive peaks from the two tasks.

stimuli. In Task B, the subject must store each nonsignal and wait to see if it recurs, while in Task A, a simple target-present-or-absent decision is made on each trial. These data support the findings of others who have shown increased P300 amplitude as a function of increased cognitive activity (Donchin et al. 1973, Friedman et al. 1975, Poon et al. 1976), as well as those who have shown the presence of late components within the P300 range in tasks involving the storage of information for task-relevant signal stimuli (Chapman 1973, Posner et al. 1973). The main difference between this study and these others is that a comparison was made between physically identical but task-differentiated nonsignals.

There are few data on late component morphology and topography in children. The morphology of the responses obtained in this study appear very similar to those of the adult, marked by, in the case of signals, large-amplitude late positive components and, in the case of nonsignals, smaller, but reliable late positive components in the latency range reported for P300 (e.g., Ritter et al. 1972, Squires et al. 1975).

There appeared to be three distinct late positive components, similar in latency and scalp distribution to the P3a, P3b and SW responses seen by Squires et al. (1975). P220-264, of similar latency to P3a, did not differ in amplitude between tasks, although it was larger to the signal (infrequent stimulus) than to the nonsignal (frequent stimulus) in both tasks. Squires et al. (1975) found P3a larger to infrequent than to frequent stimuli, whether or not these stimuli were attended or ignored. P319-352 (latency range of P3b) and P462-484 (latency range of SW) did differ between tasks, but consistently only for nonsignals. In unpublished data, Petrasek and Vaughan have also seen a relatively constant latency late positive wave (latency of 300 msec) and a second positive component, which varied with reation time.

In addition, a late negative wave, maximal at the occiput, was observed, but only in averages of signal stimuli. Late negativity has been reported by Symmes and Eisengart (1971) to be maximal at vertex (500 msec to peak) in response to a cartoon stimuli in 5-11 year old children and by Neville (1975) at left and right temporal electrodes in response to pictorial representations of common objects in 9-13 year olds; it can also be seen in the data of Kurtzberg et al. (in press) to signal stimuli in a visual discrimination task, maximal between temporal and occipital electrodes. A late negative wave was also seen in two adult subjects of Courchesne et al. (1975) when the subjects viewed quasi-random color patterns and easily recognizable black and white patterns. The functional significance of this late negative wave is not known, nor is it known whether these reported negative waves share a common generator.

In conclusion, our data are consistent with conclusions drawn from the studies of adult subjects, both in general morphology and in the cognitive correlates of the late positive components. These types of vigilance tasks are appropriate for the study of electrophysiologic correlates of cognitive activity in children and are probably suitable for the investigation of perceptual disorders in school-age children.

Summary

Visual ERPs were recorded from six early adolescents in response to numeric stimuli during two kinds of vigilance tasks. In Task A, subjects responded to the same signal throughout a block of trials. In Task B, the signal was the repetition of any immediately preceding number. The processing demands of Task B were greater than those of Task A, since in Task B the subject had to retain a short-term memory of each nonsignal in order to determine if it recurred on the

next trial. Three late positive components, P220-264 with a centro-parietal focus, P319-352 and P462-484, both with parietal maxima, were observed to signals and nonsignals of both tasks. Nonsignals elicited larger amplitude late positive components in Task B than in Task A. P462-484 amplitude was larger for signals in Task A than Task B, a difference that may be due to longer and more variable reaction times in Task B.

These results indicate an effect of cognitive processing complexity on late positive component amplitude elicited by physically identical, but task-differentiable nonsignals, and demonstrate that the morphology and cognitive correlates of the responses obtained in children of this age appear very similar to those of the adult.

Acknowledgments

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EVOKED AND SLOW POTENTIALS DURING SENSORY CONDITIONING IN AUTISTIC, MENTALLY RETARDED, AND NORMAL CHILDREN[1]

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Contingent negative variation (CNV) has been studied in retarded children and children with behavioral disorders. Walter (1969) reported the absence of CNV in autistic children. Small et al. (1971), using photographs of subjects and their parents, found CNV in autistic as well as control children. Lelord et al. (1973), coupling sensory stimuli, observed large CNVs in autistic children. Laffont (1973), coupling sound and ankle reflex, reported similar results. Low and Stoilen (1973) showed that CNV did not reflect minimal brain damage, school failure, or specific disorders. Cohen (1973) reported CNV was present to a greater degree in control children than in children with learning disabilities. Karrer and Ivins (1976b) found a small frontal CNV and lack of topographical differentiation in retardates. Otto et al. (1976) demonstrated that aphasic children showed greater positivity than control children during warning and encodement intervals. Andreasen et al. (1976) reported lack of CNV in hyperactive children. The purpose of this study was to compare the characteristics of evoked potentials (EPs) and slow potentials (SPs) in autistic, mentally retarded, and normal children.

Apparatus and procedure

Material and methods were similar to those employed by Lelord et al. (1976). The nurse who usually took care of the child was present and sometimes was obliged to hold his hands. Ag/AgCl electrodes were placed at the vertex and over the right occipital area.

Two sessions composed of 10 series of 20 trials each were used for every subject. The auditory stimulus, a brief sound (S) of 4 msec, 1 kHz, 25 dB above adult threshold was presented alone for the first 2 series (habituation: SH1, SH2). The visual stimulus, a 1200-lux flash of light (L) from a lamp 40 cm in front of the subject, was presented 800 msec after S for 8 series per session (coupled SL). S was again presented alone during the final 2 series of the second session (extinction: SE1, SE2).

Stimuli were given only when the EEG was free of artifact from head movements or muscle contractions. Many traces had to be discarded because of artifacts. Vertical and horizontal averaged EOGs were recorded, and series in which ocular potentials were larger than vertex potentials were discarded. It was not possible to record EOG in more than half the patients who would not tolerate electrodes near the eyes. Three or four sessions were required in a number of autistic and severely retarded children.

Subjects

One-hundred-twenty-five children (60 girls, 65 boys, average age = 8) were examined. Seventy had been hospitalized in a psychiatric ward for problems of varying intensity. Thirty-five had severe disorders: total or nearly total absence of speech, serious emotional problems, and IQ < 40. Thirty-five were moderately retarded (IQ > 40) with more or less severe behavioral problems. Twelve children were pupils in a special center for mental retardates (IQ between 40 and 60) with few emotional problems. Forty-three normal children were brought to the laboratory by their parents. Most were students in public schools; the youngest were still at home with their parents.

Clinical characteristics

The clinical characteristics of each child were studied by a medical and sociologic team using questions that included several response alternatives (e.g., "present," "absent," "intense"). Each response alternative constituted a characteristic. Sixty-five clinical characteristics were delineated for each child including: lack of meaningful interpersonal relationships; need for sameness; withdrawal from contact (when intense, resembled catatonia); psychomotor symptoms; speech difficulties; anxiety (with agitation); perturbed activity (when incoherent); total lack of initiative; paradoxical agility; sensitivity to noise; mood difficulties (with excitement, with depression, with atonia); eating problems; problems with bladder and bowel control; perturbed sleep; problems in sexual behavior; aggressiveness absent (directed toward others, toward self); schooling possible (impossible); absence of psychological or psychomotor anomalies; difficulties beginning after birth (at birth); neurological signs; mental deficiency (complicated, isolated); adaptation to the examining situation; IQ (>80, 60 to 80, 40 to 60, 20 to 40, <20, impossible to examine, homogeneous, nonhomogeneous, intermediate); and age (0 to 2 years, 2 to 4 years, 4 to 6 years, 7 to 13 years).

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[1] This study was supported by INSERM (C.L. 1975, 1, 205-6) Fondation pour la Recherche Medicale (S.O. 5.75), Caisse Regionale de Securite Sociale du Centre. We wish to thank J. Goldstein for his assistance in the development of this text.

Electrophysiological criteria

Event-related potentials (ERPs) were averaged for each set of 20 trials. ERPs in the habituation (SH), coupled SL, and extinction (SE) conditions exhibited different waveforms, amplitudes, and scalp localizations.

For each series, ERPs were assessed at the vertex and occipital area in three time windows: (1) from 0 to 100 msec after stimulation (early phenomenon), (2) from 100 to 400 msec after stimulation (evoked potential–EP), (3) from 400 to 800 msec after stimulation (slow potential–SP). The amplitude of each potential was measured peak to peak for responses found in the first and second windows. Amplitude relative to a horizontal baseline that passes equidistant to the extreme peaks recorded during the first 100 msec was the measure of response for the third window. In the first two windows, the potentials were generally polyphasic. In certain subjects, however, these potentials were replaced in the second window by a single early wave whose amplitude was measured from the baseline previously defined.

Amplitude values for each child were compared to mean values (m) for normal children calculated during an earlier study (Lelord et al. 1976). The amplitude of each response was taken as equal to the mean amplitude if it was within $\pm 2\sigma$ of m; larger if it fell above or smaller if it fell below m by more than 2σ.

For each child, amplitudes of responses to sound in coupled SL and extinction series were compared to those in the second habituation series (SH2). Conditioning was considered to have occurred if SL coupling augmented the amplitude of responses to sound as compared to SH2 responses. The amplitude of responses to sound and light stimuli in SL series was compared. The positive or negative polarity of SPs in the 400- to 800-msec window was also scored.

EP and SP responses at the vertex or in the occipital region were scored as "present" if the amplitude measured more than 4 μV. Responses to sound alone were considered present if they appeared in either SH1 or SH2. Conditioned EPs and SPs were defined as occurring where the response to click was larger in coupled SL trials than in SH2. Frequency of conditioned response was scored as "absent," "few" ($n < 6$ out of 16 tracings) or "many" ($n > 6$). Evoked SP of the same polarity at the vertex and occiput were considered "generalized." EP responses to light (window 2) were "regular" ($n > 12$) or "irregular" ($n \leqslant 12$); SP responses to light were "absent," "few" ($n \leqslant 6$), or "many" ($n > 6$). Some subjects evidenced rhythmic phenomena (from 7 to 13 c/sec) in response to stimulation. In certain subjects a "conditioning to time" defined as a response in the absence of light was observed during extinction. In this manner, a total of 125 electrophysiological measures were scored for each child.

Analysis of relationships

A factorial analysis of correspondence (Benzecri 1976; also cf. Bruneau et al., this volume) of electrophysiological and clinical data was done for the 125 children with a UNIVAC 1108 computer. Data were extracted from a frequency table with values between 0 and 1. The analysis then considered two multidimensional spaces. Each electrophysiological measure was situated in relation to *m* clinical axes; each clinical trait was situated in relation to *n* electrophysiological axes. Then a search of the best space directions (inertia axis) was performed. The representations of clinical traits and electrophysiological data were made *symmetrical* to allow the passage from one representation to another. The two symmetrical representations were then superimposed on a two-dimensional space. The relationships between electrophysiological data and clinical traits were expressed by the proximity of numbers and letters, which represented the two data domains, respectively.

Results

Fig. 1 illustrates the two-dimensional space of factorial Axes 1 and 2, which represented 53.5% of the information. A progression of electrophysiological factors and clinical traits could be seen along the second axis. This progression, depicted for Area I in Fig. 2, demonstrated four approximately equal bands distributed from top to bottom.

Area I was characterized by: (1) many generalized conditioned SPs to S of coupled SL, (2) conditioned

SPs larger than unconditioned SPs evoked by L, (3) SPs and EPs conditioned to time during extinction, (4) many vertex visual SPs, and (5) visual EP small at the vertex and irregular on the occipital region. Associated clinical traits were withdrawal from social contact, need for sameness, catatonia, complicated mental deficiency, and IQ between 20 and 40.

Area II was characterized by: (1) the absence of conditioned EP or SP response to S during SL coupling; (2) no rhythmical potential evoked by S of coupled SL; (3) no conditioned auditory EP during extinction; (4) during extinction, SPs and rhythmical potentials conditioned to time; and (5) small visual EPs and many visual SPs. Clinical traits included: schooling impossible, lack of meaningful interpersonal relationships, agitation, speech difficulties, excitation, nonhomogeneous IQ, and neurological signs.

Area III could be divided in two subareas: superior (a) and inferior (b). In subarea (a), there were (1) many conditioned SPs localized either at the vertex or the occiput, (2) few conditioned to time after SL. Clinical traits were IQ between 40 and 60, depression, atonia, perturbed activity, and aggressiveness directed toward others. In subarea (b), there were (1) few conditioned EPs and few conditioned SPs, (2) early phenomena, (3) regular visual EPs with average amplitude. Clinical traits included isolated mental deficiency, absence of need for sameness, absence of aggressiveness, and no perturbed sleep.

Area IV was characterized by: (1) many conditioned rhythmic potentials and EPs at the vertex and in the occipital region, (2) generalized conditioned SP absent and conditioned SPs localized at the vertex, (3) conditioned rhythmical potentials present on the occiput, (4) no conditioning to time, (5) visual EP amplitude large both at vertex and in occipital region. Clinical traits included: IQ > 80, presence of meaningful interpersonal relationships, absence of psychomotor symptoms, absence of speech difficulties, and absence of anxiety.

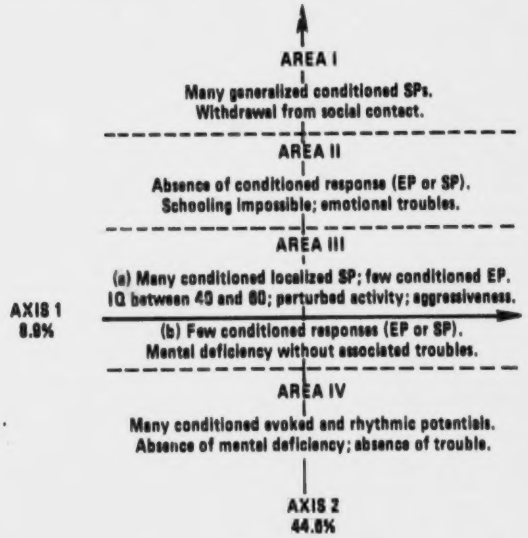
AREA I
Many generalized conditioned SPs.
Withdrawal from social contact.
AREA II
Absence of conditioned response (EP or SP).
Schooling impossible; emotional troubles.
AREA III
(a) Many conditioned localized SP; few conditioned EP.
IQ between 40 and 60; perturbed activity; aggressiveness.
AXIS 1
8.9%
(b) Few conditioned responses (EP or SP).
Mental deficiency without associated troubles.
AREA IV
Many conditioned evoked and rhythmic potentials.
Absence of mental deficiency; absence of trouble.
AXIS 2
44.6%

Fig. 1. Analysis of relationships. Two-dimensional space depicting relations between electrophysiological and clinical measures clustering as four bands or areas. EP: evoked potentials; SP: slow potentials.

The results are summarized in Fig. 3 by representative profiles from three 8-year-old children. The left column reflects Area I electrophysiological characteristics associated with clinical traits of an autistic child. The middle column represents Area IV electrophysiological characteristics of a normally adjusted child. The right column corresponds to Area III electrophysiological characteristics associated with clinical traits of a moderately mentally retarded child.

Discussion

If one considers the frequency of occurrence of EPs as a reverse indicator of variability, then Area III retarded subjects were more variable than the other groups of children studied. This result may support Callaway's finding (1973) in dull subjects. The absence of EP conditioning also confirms the observations of Shipley (1970) who recorded a facilitation in normal but not in retarded subjects when sound and light were paired.

The enhancement of SPs in autistic children was not observed in the CNV experiments of Walter (1969) and Small et al. (1971). This difference may be due to the absence of motor response contingencies and the motivational variables related to motor involvement. For instance, enhanced SPs have also been observed in experiments using ankle reflex as an unconditioned stimulus (Laffont 1973). Enhancement of SPs does not seem to be related to extracerebral artifact because the EEG during the trials was without movement or EMG artifact, and ocular movements were minimal. Eye movements were less frequent after sound (seen in 15% of the EEG tracings) than after light (seen in 80% of the tracings). Moreover, averaged SPs after coupled sound were larger than averaged SPs after light. It should also be noted that ocular potentials are generally small or absent in the occipital region. Generalized conditioned SPs, however, were recorded both at the vertex and occipital region.

A comparison between Areas I and II shows that the clinical traits of autism are related to generalized conditioned SPs. However, the clinical traits of severe mental retardation, impossibility of schooling, lack of meaningful interpersonal relationships, and excitation corresponded to the absence of conditioned SPs.

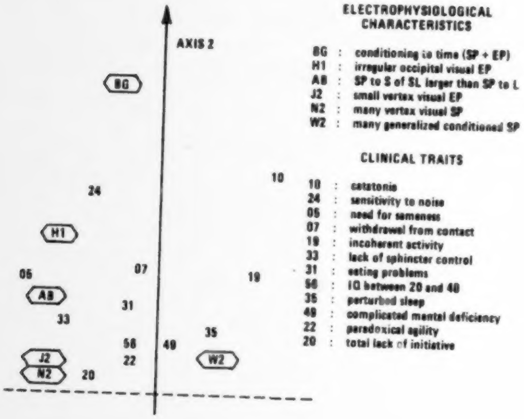

Fig. 2. Analysis of relationships (Area I of Fig. 1). The relationships were given by the proximities of letters and numbers, which respectively represented electrophysiological characteristics and clinical traits. EP: evoked potentials; SP: slow potentials; S: sound; L: light; SL: coupled sound and light.

Similar ocular artifacts are observed in both cases, while conditioned SPs, large in Area I, are missing in Area II.

Polarity of SPs tends to be negative in autistic children and positive in mentally deficient (Lelord et al. 1976). Such a positivity, observed by Karrer and Ivins (1976b) in mental retardates and by Otto et al. (1976) in aphasic children, suggests differing mechanisms related to maturation or motor overflow (Cohen 1973).

The marked presence of EPs conditioned to time is striking in Areas I and II. This particular form of acquisition, mentioned by Popov (1948), Rusinov (1959), and Lelord et al. (1967) in mental retardates, has been studied more recently under the guise of "emitted potentials" (Sutton and Paul 1973, Picton and Hillyard 1974) or "congruent potentials" (Buchsbaum et al. 1974a) in normal subjects. It appears as an enhancement of some capacity to reproduce temporal sequences in young patients.

Summary

A factorial analysis of clinical data and EEG data obtained during conditioning with sound and light was

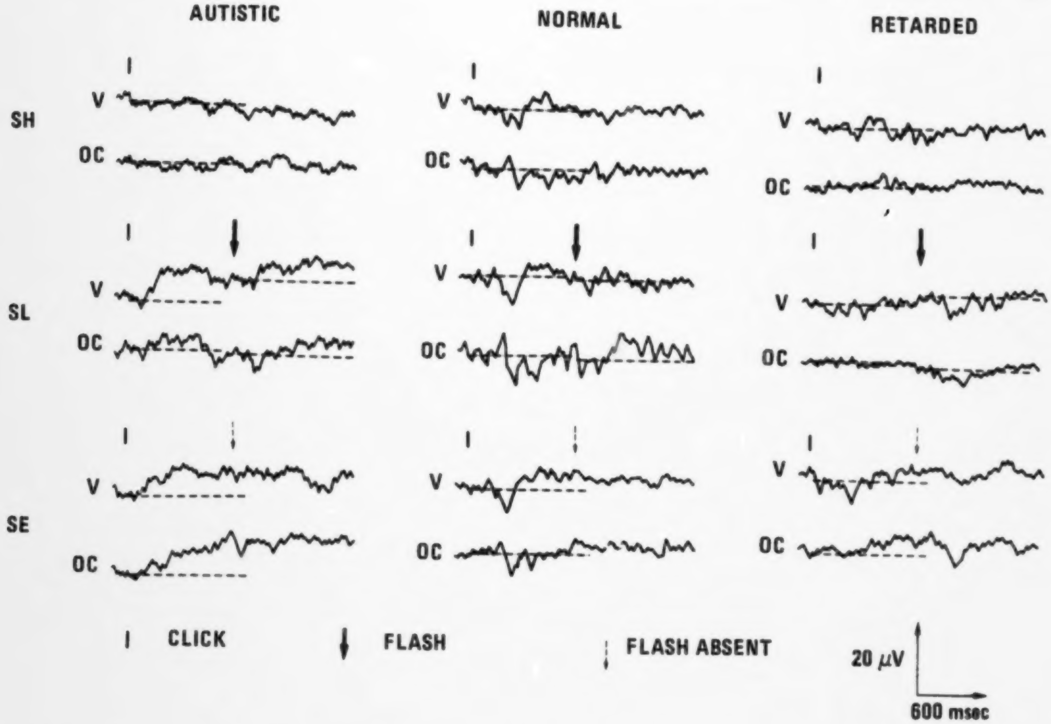

Fig. 3. Individual tracings. The three tracings summarize the principal clinical traits and electrophysiological characteristics exhibited by the analysis of relationships. To the left: an autistic child (Area I, Fig. 1); in the middle: a normal child (Area IV, Fig. 1); to the right: a mentally retarded child (Area III(b), Fig. 1). Top traces: habituation (SH); middle: conditioning (SL); bottom: extinction (SE). V: vertex; Oc: occipital.

described in 125 children (43 normals, 82 psychiatric patients). From an electrophysiological perspective, three major groups could be defined: (1) generalized conditioned SP without conditioned EP, (2) few conditioned EPs or SPs, (3) conditioned EPs and vertex localized conditioned SPs. Clinically, three major groups appeared: autistic, mentally deficient, and normal children. The relationship of electrophysiological and clinical profiles derived from factorial analysis was discussed.

CNV AND EEG PATTERNS IN CHILDREN WITH CEREBRAL PALSY AND KNOWN BRAIN LESIONS

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Weinberg and Papakostopoulos (1975) have emphasized the need to study ERP patterns in relation to the utilization of signal information for motor control, a subject to which an entire section is devoted in this volume. Patients with asymmetric brain damage, such as hemiparesis or hemiplegia which impairs motor skills, constitute a unique clinical population for such studies. Goto et al. (1973) found that slow negative potentials recorded from the Rolandic area of hemiplegic adults were greater preceding voluntary movement of the impaired limb than the healthy limb. These authors, however, did not report the extent of brain lesions, the degree of motor impairment, or the symmetry of potentials on the two hemispheres.

CNV patterns in children with focal paralysis have not been previously reported. Since the frequency of EEG abnormalities in children with cerebral palsy is high (e.g., Winfield et al. 1955), the present study was undertaken to examine the relationship of EEG patterns and the amplitude, shape and symmetry of CNV in children with this disorder. Detailed consideration of the nature and extent of lesions which may affect the symmetry of CNVs (McCallum 1972) will be given.

Methods

Six children (7 to 12 years old; four males and two females), four of whom were affected by hemiparesis, one by slight upper monoparesis, and one by slight upper monoparesis and triplegia, were examined. In all cases X-ray contrast investigation–pneumoencephalography, positive contrast ventriculography, angiography, and computerized axial tomography–was performed to determine the extent and cause of cerebral lesions. Clinical assessments of each child are summarized in Table 1.

A foreperiod reaction time paradigm was used: S1 (click)–1.5 sec ISI–S2 (moderate intensity repetitive tones)–response (terminating S2 as quickly as possible by a button press). Thirty-five trials were performed using the more skillful hand and 35 using the paretic hand. During the session, children gazed at a black fixation point on a mirror. A Grass 10-channel ac-dc polygraph having a 6-sec time constant was used to amplify EEG data. Ag/AgCl electrodes were placed over C3, C4, and Cz and referred to linked mastoids. Electrodes above and below the eye were used to monitor vertical EOG. In some cases, EEG recordings were obtained from C3 and C4 referred to ipsilateral mastoid and Cz referred to linked ears. Finger photoplethysmograms, electromyograms from the muscles and limbs involved in synkinetic movements, and reaction times (RT) were also recorded. Polygraph data were averaged on-line with a signal analyzer and stored on analog tape for off-line averaging of selected trials (without eye movement artefacts). The amplitude of each CNV (8 to 16 trials) was measured from baseline to points at 50, 100, and 150 msec preceding the onset of S2. Baselines were defined as the average amplitude of EEG activity 800 msec preceding S1. Experimental procedures have been detailed elsewhere (Zappoli et al. 1973).

Results and discussion

In spite of restlessness and motor impairment, CNVs were obtained from all children, and more than 35% of the trials, without movement or other artefacts, could be averaged. In some cases, the response proved difficult owing to the hemiparesis, and was only performed with motor involvement of the whole limb. S6 was able to respond only with the paretic hand as the other was plegic. S3 presented pathologic synkinetic movements of the hemiparetic limbs when responding with the good hand.

Vertex CNV voltage ranged from 8.3 to 40 μV. The group mean amplitude of artefact-free vertex CNV was about 24 μV during unimpaired limb performance and 26.5 μV during impaired hand performance. This difference resulted from two subjects who showed a

Table 1. Clinical Description of Subjects

S	Sex	Age	Motor impairment	Epilepsy	EEG abnormalities	Diagnosis
1	M	9	R hemiparesis	R focal	R normal; L focal paroxysm. activity	Hemispheric atrophy
2	M	10	R hemiparesis	R focal	R normal; L focal paroxysm. activity	Hemispheric atrophy
3	F	9	L hemiparesis	R focal	R flat; L focal paroxysm. activity	Hemispheric atrophy, especially R
4	F	7	R hemiparesis	----	Almost continuous slow wave pattern	Tumor of the brain stem
5	M	12	R slight upper monoparesis	R focal	Diffuse paroxysm. activity	Slight l. Cerebrovasc. disorder
6	M	12	Triplegia; L slight upper monoparesis	L focal	R focal paroxysm. activity; L flat	Hydrocephalus; malfunction of the spinal cord

marked difference in skill between the two hands (slow RT with the paretic and fast RT with the healthy hand). These subjects showed no synkinetic movement when using the unimpaired hand. No differences in vertex CNV or in RT were apparent in subjects who presented synkinetic movements.

Analysis of amplitude asymmetries between C4 and C3 indicated that the less impaired hemisphere showed higher mean voltage CNV ($\overline{x} = 29.8$ vs. $18.2\ \mu V$) when the less impaired limb responded (e.g., Fig. 1). The only subject who presented no asymmetry in C3 and C4 CNV amplitudes during less impaired hand performance was a child (S5) with slight monoparesis and diffuse paroxysmal EEG abnormalities (who successfully recovered). During trials in which the impaired hand was used (five cases–S6 excluded due to paralysis), mean CNV voltage was much lower in the impaired ($14\ \mu V$) than less impaired hemisphere ($31\ \mu V$) in every subject.

Goto et al. (1973) have suggested that voltage enhancement occurs in the less impaired hemisphere due to compensation. Alternatively, the asymmetry may be due to the brain lesion and consequent dysfunction in the electrogenesis of slow potentials (cf. McCallum 1972).

CNV morphology often showed a marked difference between C3 and C4. The shape of the CNV in a hemisphere was often constant and independent of amplitude. Three CNV patterns were apparent: (1) normal CNV (Fig. 2A); (2) a small, smooth CNV with a slow ascending limb, often preceded and followed by smooth poststimulus positivities (Fig. 2B); and (3) a large, irregular saw-toothed and sharp pattern with deep and rapid high voltage (up to $40\ \mu V$) poststimulus positivities (Fig. 2C). Differences were more evident in raw recordings than averaged CNVs.

The first pattern was recorded over apparently healthy hemispheres. The second CNV pattern was recorded mainly from hemispheres with neuroradiological signs of marked cerebral atrophy and flat EEG activity, or signs of a subcortical tumor and continuous slow wave EEG patterns. The third type was recorded from hemispheres with marked EEG paroxysmal discharge and, at times, slight atrophy of cerebrovascular origin. Thus, asymmetries in CNV shape seem to be related to the type of pathology and spontaneous EEG activity of the two hemispheres.

In normal adults, symmetric CNVs are usually produced by the two hemispheres regardless of which hand performs (Weinberg and Papakostopoulos 1975). In children with asymmetric brain lesions and motor impairment, a marked asymmetry in shape and amplitude was recorded. Asymmetry in shape seems to be related to the spontaneous bioelectrical activity of the hemispheres, while asymmetry of amplitude seems to be related to the impaired hand performing.

Central areas seem to be involved in the efficient utilization of information for skillful performance (Papakostopoulos, this volume). The above data suggest that processes of less impaired areas are involved in the functional balancing of more impaired areas in order to enhance motor control when the more impaired limb is required to perform.

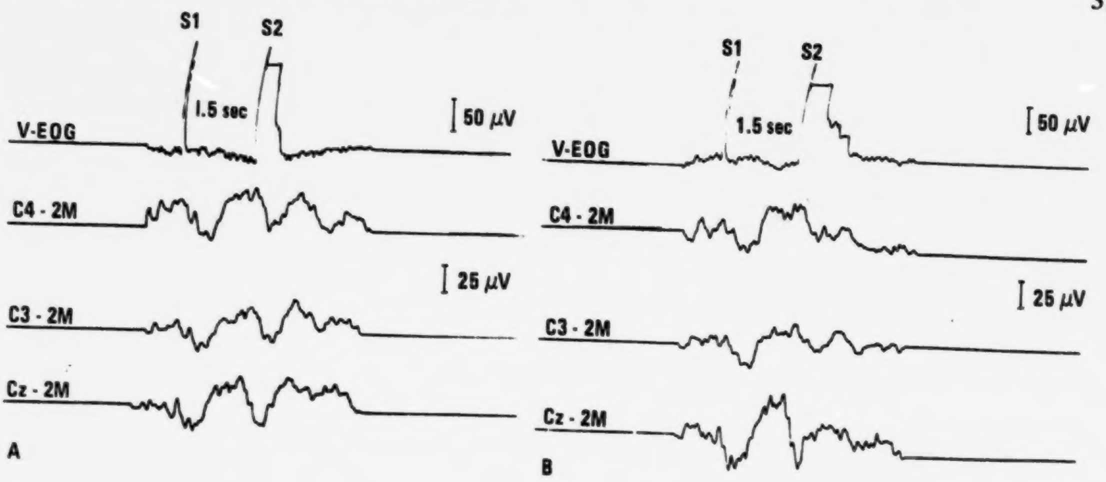

Fig. 1. Amplitude asymmetries in subject 4, right hemiparesis. A: Averaged responses to eight artifact-free trials using left (unimpaired) hand. CNV followed by postimperative negative variation (PINV) in all derivations. CNV amplitudes: C4 = 22.2 µV, C3 = 19.4 µV, Cz = 25.2 µV. Mean RT = 325 msec. B: Average of eight right (impaired) hand trials. CNV amplitudes: C4 = 24.8 µV, C3 = 18.8 µV, Cz = 34.3 µV. Mean RT = 480 msec. Less evident PINV. VEOG = vertical electrooculogram with superimposed S1 and S2; 5-sec epoch. C4, C3, Cz referred to linked mastoids (2M). Baseline = 800 msec before S1; Negative up.

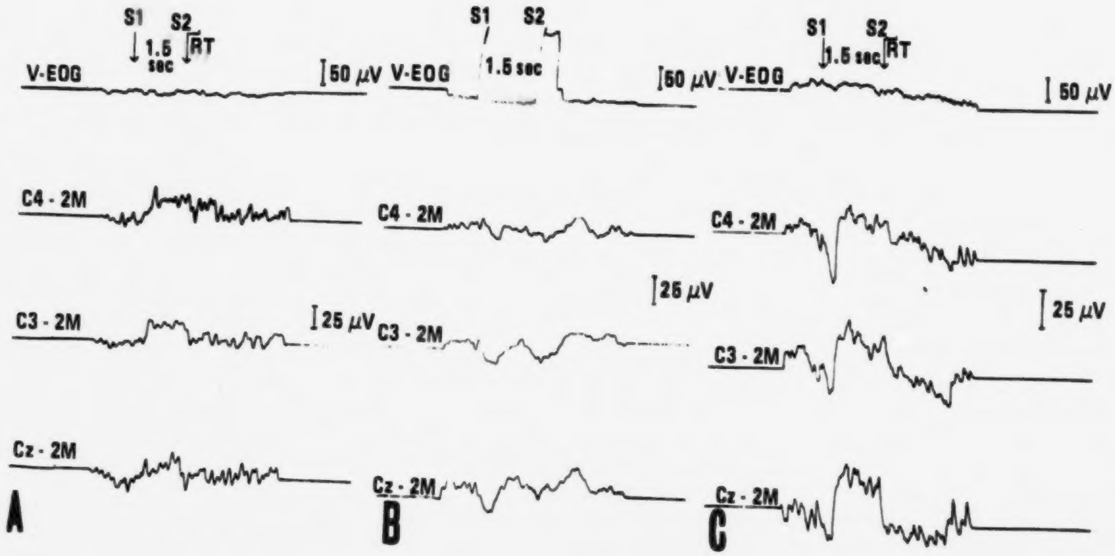

Fig. 2. Shape differences. A: Subject 5. Marked difference in CNV shape between the two hemispheres. In C4, note slightly sharper CNV of the healthier hemisphere and in C3, slightly smooth CNV of the more impaired hemisphere. The main difference seems to be in the abundance of superimposed rhythms. B: Subject 4. Smooth CNV with a slow ascending limb preceded and followed by evident smooth poststimulus positivities. C. Subject 3. Irregular, saw-toothed, and sharp CNV with deep and rapid high voltage post-S1 positivities. (Same abbreviations as Fig. 1).

SLOW POTENTIALS OF THE BRAIN PRECEDING CUED AND NONCUED MOVEMENT: EFFECTS OF DEVELOPMENT AND MENTAL RETARDATION

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There has been little study of slow potential (SP)-behavior relationships during normal development or in the mentally retarded (MR). Such information could provide insight concerning cognitive and motor development, as well as further specify the linkage between scalp recorded potentials and behavior. Karrer and Ivins (1976a, 1976c) demonstrated an inverse relationship of post-warning signal positivity (PWSP) at Cz and Fz to age and to the manipulation of reaction time (RT). Preadolescent children showed larger PWSP than adolescents, and warning signals that resulted in faster RTs were associated with larger PWSP. We speculated that the larger PWSP in young children may be a reflection of inhibitory processes utilized to organize a motor act and facilitate a subsequent motor response set. Papakostopoulos and Crow (1976) hypothesized that a component after the response signal, the late positivity (P300), may also be related to inhibitory motor processes.

Karrer and Ivins (1976b, 1976c) also found that adolescent MRs had more PWSP than age-matched normals, but less than preadolescent children. Following the above interpretation, the MR may need to mobilize inhibitory processes to a greater extent than normal age mates. On the other hand, no differences in CNV amplitude were found between these groups in a RT or perceptual task. The MR, however, did not always reflect the same relations of SP activity to performance as did age-matched normals. Most notably, the timing and topography of SP activity were different from that of normals, suggesting a different organization of cortical events associated with behavior.

Otto et al. (1976) reported SP data in normal and learning disabled (LD) children (aphasics and dyslexics) performing pictorial and letter-matching tasks. The results appear consistent in some respects with the findings cited above. Following a warning interval, information was presented at S2 and S3, to which subjects made same/different matching responses. During both the warning and encodement intervals, positivity at Cz was found to be inversely related to age in normal groups. Moreover, LD children showed slower RT and greater positivity at Cz than normal children during warning, encodement, and response intervals. Positivity became greater prior to S3 (the point at which letter matching and decision was required) and became even larger prior to the response, by which time matching and decision may be assumed to have been completed. The slower RT and increased errors in the LD group indicated that the matching decision was more difficult (i.e., more uncertain), and took longer than for normals. Probably because of task requirements, the locus of SP differences was late in the epochs, instead of early as found by Karrer and Ivins (1976c).

The present paper is an interim report of SP activity preceding simple movement during development in normal and retarded children. A simple RT task with well-known developmental differences was used (normal children and MR adolescents are slower than normal preadolescents or adolescents). In addition, the traditional motor readiness potential, or Bereitschaftspotential (BP), task of a simple noncued voluntary movement was employed. If the young child's preparation to respond requires greater inhibitory effort to control irrelevant motor behavior, then there should be positive components within the BP not apparent in the motorically developed adolescent. Since the child is slower than the adult or MR in RT, reflecting less organized motor processes, premotion negative potentials were expected to begin later in the interval preceding movement (Karrer and Ivins 1976c).

Analogous differences in positivity were predicted for the MR. Further, the MR should exhibit a different organization of neural events reflected by differences in topography and timing of potentials preceding movement when compared to age-matched normals.

Finally, it was predicted that SP differences between the MR and normal subjects would be larger when performing a cued response as opposed to a voluntary noncued response. This expectation was based upon previous work (Berkson 1960, Clausen 1966), implicating response initiation as an important factor in slow reaction time of the mental retardate.

Method

Subjects

Data were gathered from 12 (8 in cued task) children ($\bar{X}$ age = 7.4 yr), 11 preadolescents ($\bar{X}$ age = 12.6), 13 adolescents ($\bar{X}$ age = 18.0), and 11 MR adolescents ($\bar{X}$ age = 17.7). All were male. Mean IQs of the group were 105, 110, 118, and 65, respectively. MRs had no diagnosed neurologic impairment (except one Down's Syndrome) and were students at special education facilities. All but one preadolescent and one adolescent were right handed.

Procedure

Activity preceding movement was recorded during a nonwarned simple reaction time (RT) task and a noncued voluntary button press task. In both conditions, subjects responded (R) by pressing a button with his dominant thumb. In the RT task, the response cue was a flash from a Grass Photostimulator (intensity = 8). The flash was reflected off a 38-in. diameter opaque Plexiglass hemisphere. The average intertrial interval was approximately 14 sec, and varied roughly ± 4 sec. Subjects were instructed to respond as fast as possible to the flash. They sat 2 ft in front of the hemisphere and were requested to refrain from blinking or making other eye or body movements. For the noncued response condition, subjects were asked to make a series of responses separated by about 2 to 5 sec. They were required to fixate on a point at the center of the hemisphere while at least 50 trials were collected for each task in one or two sessions.

Recording

Beckman nonpolarizing electrodes were placed at Oz, Cz, C3, C4, and Fz referred to linked-ear electrodes on the inner earlobes for dc recording with a Grass (Model 7) Polygraph and Ampex (Model 1300) FM recorder. Electrodes above and below the left eye were separately referred to linked ears for two monopolar recordings. Simultaneous deflections of opposite polarity on these two channels indicated an eye blink or movement. EMG activity was measured from the responding and contralateral thumb and summed by means of a Grass integrating ac amplifier.

Data reduction and analysis

The data were digitized, edited, and averaged on a PDP 11/10 computer at 4 msec/point, with trials contaminated by excessive drift, unstable baselines, or sudden dc changes excluded. Excluded trials were tallied separately if an eye movement or blink occurred: (1) during the epoch prior to or 200 msec after R; and (2) from 200 msec after R to the end of the epoch (600 msec after R, cued; 320 msec after R, noncued). Trial salvage rate for cued and noncued response was 42% and 21% for children, 49% and 36% for preadolescents, 72% and 63% for normal adolescents, and 70% and 44% for MRs, respectively.

Averages were generally time-locked to EMG onset in the responding thumb. The absence of thumb EMG in five MRs necessitated locking to the response, and for all groups there were occasional trials with severe EMG attentuation. These trials were assigned the mean EMG onset time of the remainder of trials. Comparison of EMG and response-locked averages indicated essentially identical waveforms. Averages time-locked to stimuli were also computed for the cued response condition for comparison of stimulus-locked and EMG-locked activity.

In the cued response task, the mean voltage of the 200-msec interval before the stimulus was used as baseline. Positive and negative voltage (V) deviations from baseline between stimulus onset and 500 msec after the response for each trial were calculated by the formula, $\Sigma V/4N$, where N is the number of points summed, which gave the mean μV/msec. In the noncued task, the μV/msec was computed from 600 msec to EMG for each subject; the voltage was relative to a baseline calculated from 800 to 600 msec prior to EMG.

Results

Noncued response

Inspection of waveforms (Fig. 1) of the young child and the retardate showed considerable deviation from the usual BP of the adult. There was also considerable variation within groups. The normal adolescent's predominant waveform was similar to an adult BP; a slow negative shift commenced about 500-700 msec before EMG onset and reached a steeper peak about 150 msec after the button press. The amplitudes were smaller, or positive, in Fz and Oz. One-third of the adolescents did not show a discernible response over central areas.

The waveform of young children was more complex than the adolescent waveform with at least two to three prominent features, depending on the recording site, prior to the response. There was an initial positivity (Oz, Cz, Fz) starting 600-650 msec prior to EMG, followed by a prominent negative shift (3-5 μV), and peaking 150-350 msec prior to EMG. A second prominent (Cz and C4) positive shift (5-6 μV) peaked

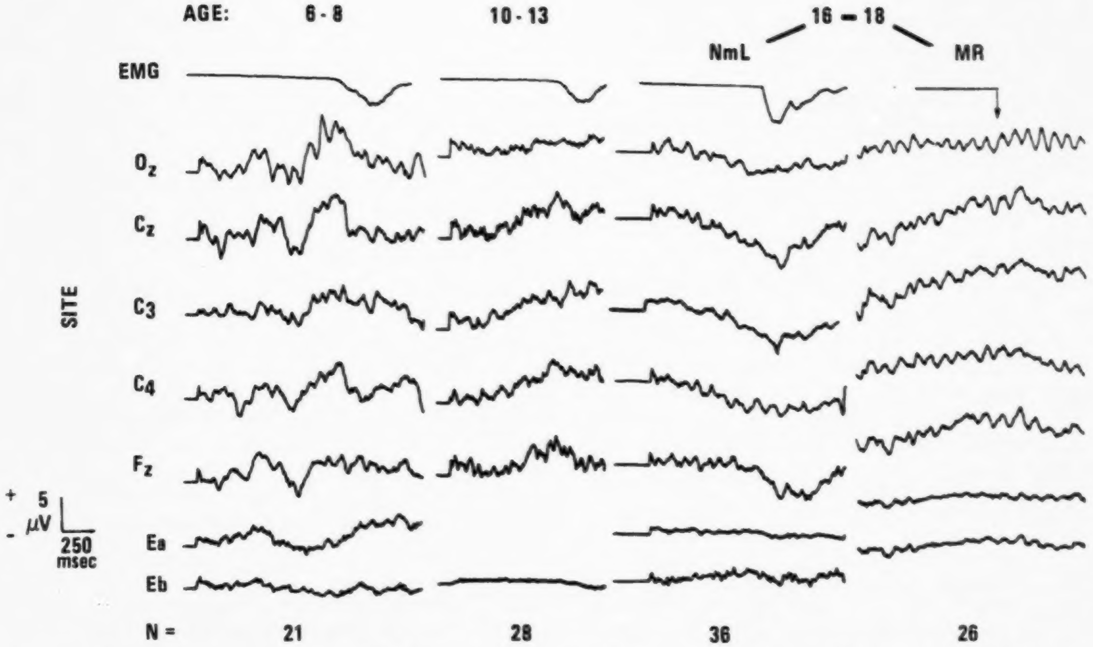

Fig. 1. Average activity for one subject in each group, showing representative waveforms and distributions for the noncued task. Note lack of associated activity in the eye below lead (Eb). Positive is up. Gain for eye above lead (Ea and Eb) is ½ EEG. N = number of trials in average. NML = normal.

near the onset of EMG and was followed by a slow return to baseline. Some averages appeared to reflect low frequency activity, predominant at age 6-8 (Lairy 1975), and, therefore, probably were not time-locked to the response. Only a small proportion exhibited the adult waveform (Fig. 2).

Preadolescents exhibited the greatest waveform variation: 27% exhibited the complex waveform characteristic of young children; 35% exhibited a unique monophasic positive wave, peaking at or before EMG onset; and 18% showed normal adult waveforms. This mixture reflects the transitional nature of the group in motor development and emergence of associated EEG patterns.

The predominant MR waveform was a long slow positivity (4-10 μV), beginning about 800 msec prior to EMG and returning slowly to base level after response. Sometimes, a slight negativity occurred midway in the positivity, resembling the waveform of a young child. As with adolescents, one-third of the MRs failed to show a discernible response over central areas.

Fig. 2 shows idealized representations of observed waveforms, the proportion of subjects showing each, and a representative average of one subject from the modal group characterized by the waveform. Waveform classifications were derived from visual inspection of Cz recordings of all subjects by two judges. Chi square analyses of the proportion of the four waveforms (ignoring the rhythmic activity and no-response subjects) were performed between groups. Adolescents and MR were significantly different ($\chi^2 = 10.5$, df = 3, $p < .01$) as were the three normal groups ($\chi^2 = 33.7$, df = 6, $p < .001$).

Statistical evaluation (Mann-Whitney U-Test) was performed on the μV/msec measure of those MRs and normal adolescents showing the predominant MR and adolescent waveform (excluding all other waveform types). Fig. 3 depicts these relations. These selected groups differed significantly, indicating that the retarded had greater positivity in all leads (U=3, 0, 8, 2, 5, $p < .05$, respectively, for Oz, Cz, C3, C4, and Fz).

As a measure of irrelevant motor behavior, the ratio of the number of trials discarded as a result of eye movement divided by the number of trials completely free of eye-movement contamination was determined for each eye-movement category and individual. This ratio of preresponse eye movement to otherwise good trials for children, preadolescents, and retardates was greater than for adolescents (U=17, 26, 34, $p < .05$, respectively). Children, preadolescents and retardates, however, did not differ on this ratio. EMG of the nonresponding thumb did not provide a useful measure of irrelevant motor behavior because of the low incidence of measurable activity.

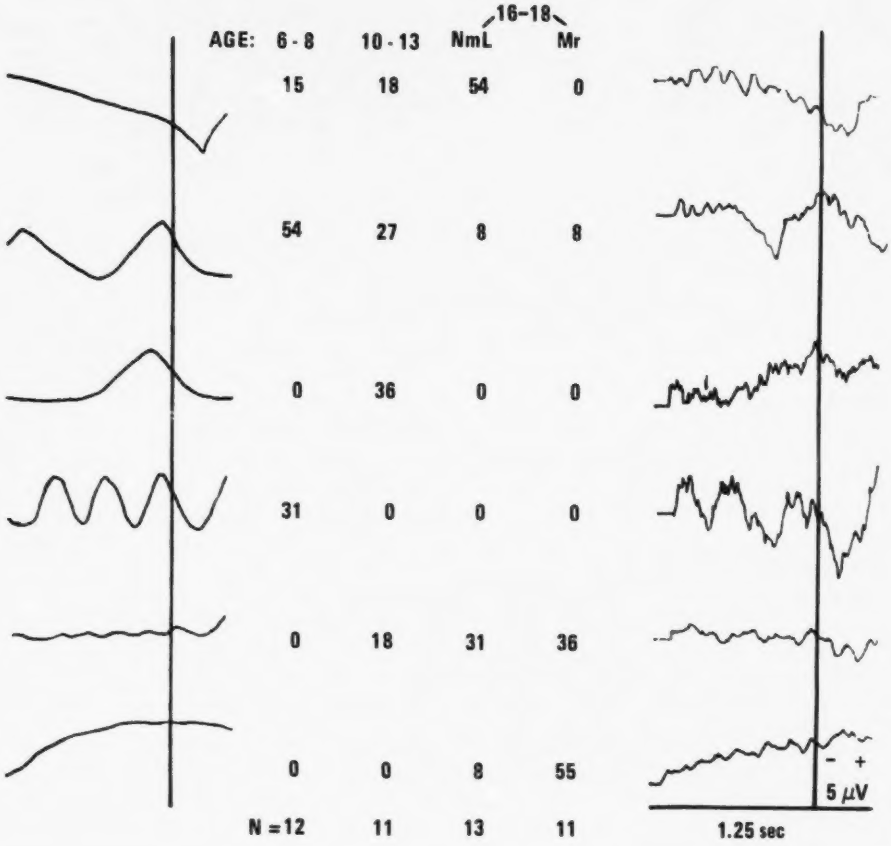

Fig. 2. Idealized Cz waveforms (left), percentage of subjects showing waveform in each group (middle), and a representative subject's average (right) for the noncued button press. N = number of subjects per group. Positive, up.

Correlations of preresponse and postresponse eye movement ratios to μV/msec, prior to the response, were calculated for each recording site within each group. None were significant for *postresponse* eye movement. All significant correlations were for the *preresponse* eye-movement exclusion category. One correlation was found to be significant in the 6- to 8-year-old group ($r = 0.60$, $p < .05$ for C4). There were two significant correlations in the MR ($r = 0.64$, -0.65, $p < .05$, for Oz, Fz) while the correlation for C4 approached significance but in the opposite direction ($r = -0.54$). There were no significant correlations for the preadolescents or adolescents. These relations indicated that, for children, the greater the ratio of rejected trials to retained trials, the larger the positive (less negativity) at C4 on retained trials. In the MR, larger ratios were associated with larger positivity (less negativity) at Oz, but less positivity (more negativity) at Fz.

Cued response

An ANOVA of RT between groups revealed a significant difference ($F\ 3/44=5.27$, $p < .003$). RT was slower in MR ($\overline{X}$=417 msec) and children ($\overline{X}$=451 msec) than in adolescents ($\overline{X}$=275 msec). Children (N=8) were also slower than preadolescents ($\overline{X}$=322 msec).

Examples of waveforms in each group are shown in Fig. 4. The averages of activity time-locked to EMG onset show different amplitudes and waveforms across ages and MR. There is little evidence of the VEP in these averages, indicating that the variability of response is sufficient to cancel the VEP. Children and preadolescents exhibited a definite slow-rising positivity, peaking at or after EMG onset, although RT ranged from 250 to 750 msec. This positivity was often preceded by a negative-going component (not

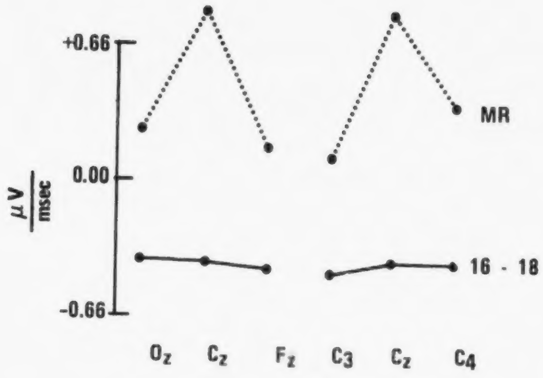

Fig. 3. Mean μv/msec SP value for those subjects exhibiting modal waveforms for normal and retarded adolescents across recording sites for noncued task. Pre-R refers to measurement epoch.

seen in Oz) that was larger in children than the other groups. This negative-positive waveform is somewhat similar to that found in the children's noncued waveform. In general, the MR had waveforms similar to normal adolescents, who had only small positivies associated with EMG onset.

A repeated-measures ANOVA (Groups and Leads) of the μV/msec measure indicated that a leads effect and groups x leads interaction were significant (F 4/152=26.4; F 12/152=3.8, $p < .001$, respectively. The predominant polarity exhibited by the child was significantly more positive than that of the adolescent or MR at Oz and Cz (U=6, 5, Oz; 3, 6, Cz).

Significant correlations between SP and RT measures were found in adolescents at C4 (r=0.70), in preadolescents at Fz (r=0.66), and in MR at Oz and Fz (r=0.86, -0.85, respectively). There were no significant correlations in children, but all were the same sign as in the MR and approached significance in Oz and Fz. Further, correlations of RT across tasks to SP in the noncued task indicated no significant correlations in the normal groups. For the retarded, however, activity in Cz, C4 and Fz was related to RT (r=0.65, 0.61, 0.65, $p < .05$, respectively).

Comparisons of the ratio of rejected eye-movement trials to good trials indicated that children, preadolescents, and MR had greater ratios than adolescents, but only preadolescents were significantly greater (U=20, $p < .02$). Groups were again compared on correlation of these ratios of rejected eye-movement trials (as an index of irrelevant motor activity) to SPμV/msec. As in the noncued task, there was, again, a significant correlation in children for C4 (r=0.62). There were no other significant correlations.

In contrast to the average time-locked to EMG, the average time-locked to the stimulus showed large VEP

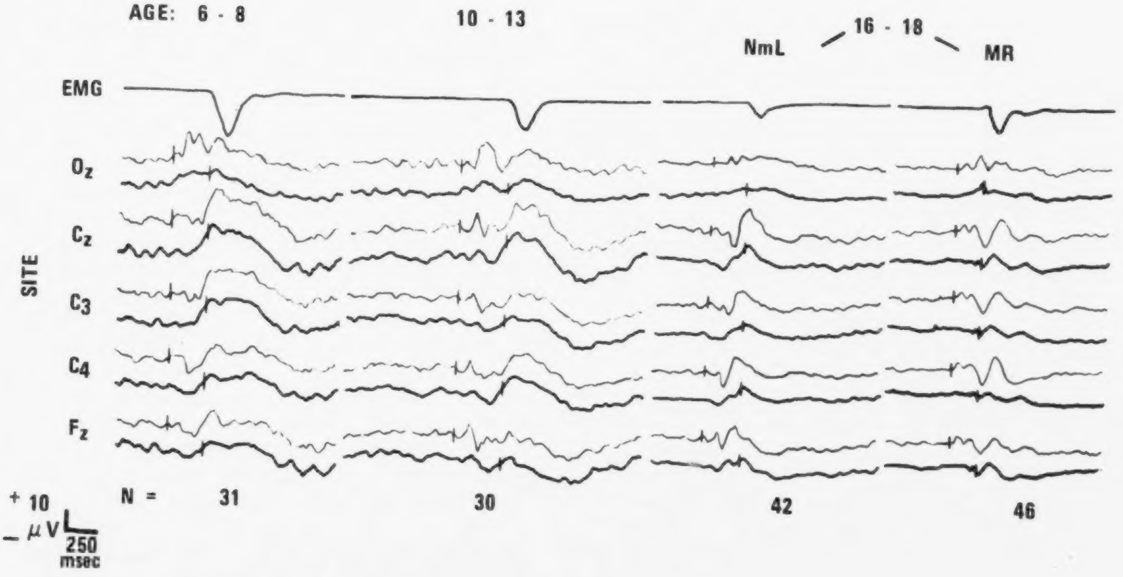

Fig. 4. Average activity of one subject in each group showing representative pairs of waveforms from each recording site for the cued task. Upper waveform of each pair is stimulus time-locked; lower waveform of pair is EMG time-locked. Positive, up. Vertical lines indicate stimulus and EMG events.

components (Fig. 4). This finding indicates that locking to the EMG (or response) maximizes components associated with movement and minimizes stimulus events. There was a lateral difference in the size of the positivity found by response-locked vs. stimulus-locked averages that changed with age and MR. Table 1 shows the difference between C4 and C3 in maximum peak negativity to peak positivity associated with EMG. Children had maximum positivity at C3 when activity was EMG-locked but at C4 when stimulus-locked. Preadolescents, MR, and normal adolescents had greater positivity at C4 than C3, regardless of time-locking.

Table 1. Difference in Peak Negativity to Peak Positivity

(C4 - C3 in μV)

	Normal children			Retardates
	6-8	10-13	16-18	16-18
STM-l	3.0	1.9	3.8	1.4
Rsp-L	-1.4	2.2	1.7	1.6

Discussion

The main features of adolescent movement-related potentials were consistent with adult waveforms (Gilden et al. 1966; Deecke et al. 1969, 1973; Vaughan et al. 1968). There was a clear, slowly increasing negativity (N1), beginning about 800 msec prior to EMG. Peak negativity (N2) usually occurred well after EMG onset. No obvious premotion positivity (PMP or P1) was apparent, although there were small positive components (noise?) in some averages. Although there was a postresponse positive-going component (P2) that terminated the waveform around the baseline, it did not consistently overshoot baseline. It is probable that the lack of a well-defined SP in a third of the adolescents was a function of the reduced signal-to-noise ratio obtained with the reduced number of trials employed. There is considerable variability in waveform within, as well as between, age groups.

The literature indicates that there is considerable variability in the presence of PMP, timing of N2, and amplitude of P2. P2 varies in size and slope and may be dependent upon the nature of the response (Deecke et al. 1969, Fig. 6) and the time constant of the recording system. Variability seems to have been ignored in favor of "the" BP waveform (compare waveforms and timing of components in Deecke et al. 1969, Fig. 2, 5; Gerbrandt et al. 1973, Fig. 4; Hazemann et al., this volume, Fig. 1; McCallum, this volume, Fig. 2; Papakostopoulos, this volume, Fig. 1; Vaughan et al. 1968, Fig. 2, 3).

The presence of positivity in children's waveforms, the similarity of waveforms in both tasks, and the existence of significant positivity-irrelevant motor activity relationships for both tasks confirms our initial hypothesis (Karrer and Ivins 1976a, 1976c). Irrelevant motor activity in the child reflects the lack of motor differentiation. Positivity seems to accompany successful inhibition of such activity. The more the child exhibits eye movement when instructed not to do so, the greater inhibition (positivity) he must develop to control eye movement to produce a "good trial." More inhibition of contralateral than ipsilateral-irrelevant movements may be required since correlations were significant only for C4. Right-hand response required inhibition of response on the left side. Contralateral inhibition of "motor overflow" develops slowly and is often undeveloped in adolescents for various hand movements (Abercrombie et al. 1964, Cohen et al. 1967, Stern et al. 1976).

Some portion of SP positivity in children may serve the same function as the PMP described by Deecke et al. (1973). A requirement of greater activity in the parietal and other association areas for initiation of a coordinated button press could account for the larger positive potentials observed in children than in adolescents. This waveform may have phylogenetic, as well as ontogenetic, significance. Donchin et al. (1971) observed in monkeys a transcortical SP complex, preceding a noncued lever press (cf. their Fig. 10), which bears a striking resemblance to the modal waveform observed in children. The second positive component observed by Donchin et al. was more prominent in central than in frontal areas. In children, this component was more noticeable at Cz and C4 than at Fz and was more pronounced than that observed by Donchin et al.

The predominantly positive waveform of the retarded in the noncued task is even more divergent than that of the child from the normal adult waveform. Lelord et al. (1976) and Laffont et al. (this section) also report positivity in young, severely retarded children during sensory conditioning. These prominent positive waveforms, therefore, may reflect immaturity or impairment of sensorimotor development, although it is not clear what sensory conditioning tasks have in common with self-paced motor tasks. Deecke et al. (this section) report a similar positive-going BP in elderly subjects. These authors suggest that this waveform may be due to the pickup at the linked-ear reference of activity arising from basal temporal cortex. We have observed that, in normal children, the ear is essentially quiet when referred to nose-tip or midchest. Therefore, it is unlikely that the positivity in the child is due to an active ear reference. Although we have not directly assessed this possibility in retardates, the monopolar infraorbital lead may be considered a control for ear activity. This lead was essentially flat, indicating an indifferent reference. It is obvious that inhibitory processes express themselves via different waveforms and topography as a function of age, retardation, and performance.

An intriguing possibility is that positivity in the MR may reflect subtle abnormalities in pyramidal motor neurons. For instance, differentiation into mature dendritic spines is arrested in the retarded individual (Huttenlocher 1974; Purpura 1974, 1975). Primitive spines are retained, and there is a severe reduction in the total number of spines. The retarded child may also have a significantly *greater* number of total cortical synapses (Cragg 1975). These facts suggest a different, less efficient synaptic geometry in retarded children. Since negative SP activity is considered to reflect, in part, activity in apical dendritic fields (McSherry 1973), the atypical positive BP of the MR may reflect the altered spatial distribution of synapses in central motor areas. If these speculations are correct, the BP could yield information about cortical synaptogenesis in the retarded and the normally developing child.

The data confirm our predictions of a different neurobehavioral organization in MR; i.e., topography and SP relations to behavior were different. MRs apparently do not generate contralateral inhibition: the correlation between eye movement and SPs was not significant and was negative in C4. In contrast to age-matched normals, MRs generated more positivity in posterior regions and less positivity in anterior regions when inhibiting eye movement. This more diffuse and topographically different pattern of SP activity, accompanying inhibition of irrelevant movement was associated with poor performance. Compared to normals, MRs exhibited higher correlations of RT to posterior and anterior SP activity in the cued task; greater Oz positivity and greater Fz negativity accompanied slow RT. Poor performance in the cued task was also related to a different diffuse pattern of positivity at central, right, and anterior areas in the noncued task; slower subjects had greater positivity. The relations of SPs to behavior are obviously different from normal groups (although the trends in children were often in the same direction).

The presence in the cued task of positives in conjunction with response onset may be similar to transcortical positivities found by Donchin et al. (1971) to accompany cued lever press. The central-postcentral area was also found to elicit larger positivities than the frontal area. The different lateral topography of positivity with age and event-locking may reflect the role of the nondominant hemisphere in sensory spatial appraisal of the flash (larger positivity in C4 for stimulus-locked averages) and the role of motor components in EMG-locked averages (positive in C3 for children but more negative in C3 for normal adolescents). This lateral relationship was essentially the same for preadolescent normals and adolescent MR. These data again indicate the value of comparing forward and backward averages (Karrer and Ivins 1976c).

It was assumed that the retardate would be more similar to normal in the noncued task, where there was no requirement to initiate a movement quickly. In the cued task, by contrast, a response had to be quickly initiated upon demand, and differences were predicted between SP activity of normal and MR adolescents. Counter to these expectations, the MR differed most from the normal adolescent in the noncued task, but were similar in the cued task.

Contrary to previous findings (Karrer and Ivins 1976c), the amplitude of positivity correlated directly with RT in the cued task. This difference may be explained if one assumes that the process of actively inhibiting irrelevant movement is incompatible with rapid response. A preparatory interval, in which subjects could inhibit irrelevant movement after receiving the warning signal, was employed in the earlier study. In the present nonwarned task, both the inhibition of irrelevant movement and the preparation for response had to occur after the imperative signal. Hence, the greater the effort needed to inhibit irrelevant movement (larger positivies), the slower the RT.

Our results and those of Otto et al. (1976) indicate that differences in level of functioning affect SP waveform and topography. The range and type of idiosyncratic or idiopathic variables that influence SP activity, however, is poorly understood. The moderately retarded, who exhibit great variability in behavior (Baumeister 1968), must utilize a variety of combinations of underlying processes, which are reflected, presumably, in great variation in the polarity and topography of slow potentials from task to task.

The large positive shifts observed in young children, elderly subjects, retardates, and other primates may reflect a common underlying inhibitory phenomenon. In primates, children, and MR, the inhibitory phenomenon could be associated with the phylogenesis and ontogenesis of motor control mechanisms. In older adults and the mentally retarded, the inhibitory phenomenon could be associated with declining or deficient motor control. The relationship of positive SPs and inhibitory processes is further discussed by Marczynski in the Electrogenesis section and by Papakostopoulos in the Motor Control section of this volume. Further research is needed to elaborate and validate these hypotheses.

Acknowledgments

We wish to express our appreciation to Anthony Morrelli and Dr. Robert Baldauf of the Oak Park, Illinois, schools, Ronald Sterrett of Samuel Kirk Center, Palatine, Illinois, and Donald Zingrabe of West Leyden Township schools, all of whom facilitated access to children. We are also grateful to Joan Gillet, Dick Mills, Jim Griffith, John Helton, and Cynthia Armstrong-Scharf for assistance in data collection, organization, and analysis. This work was supported by the Illinois Department of Mental Health and Developmental Disabilities and NICHD Grant No. HD 08265 to the senior author.

AGE-DEPENDENCE OF THE BEREITSCHAFTS-POTENTIAL[1]

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The slow negative shift of the cortical dc potential that occurs in the foreperiod of voluntary, i.e., self-paced, movement (Bereitschaftspotential, BP, or readiness potential, Kornhuber and Deecke 1964, 1965) has been studied mainly in young adult subjects. CNV research has been conducted on an older age group (Loveless and Sanford 1974), but no such investigations have been reported concerning the BP development in these groups. The present study was conducted in order to obtain a normal control group, similar in age distribution to a group of patients with Parkinson's disease in which the BP was nearly absent (Deecke et al. 1977).

Methods

Subjects were neurological clinic patients with non-cerebral diseases, e.g. slipped discs. All were right-handed. Five age groups were selected: I derived from 34 previous experiments (17-29 years); II (30-39 years); III (40-49 years); IV (50-59 years); and V (60-69 years). Groups II-V each consisted of six subjects (usually three females and three males), three performing right-sided and three left-sided voluntary index finger flections by pulling the trigger of a pistol. Movement onset was defined as the very first EMG activity in the agonist muscle (*M. flexor digitorum communis, pars indicis*). EMG, recorded through bipolar surface electrodes, was rectified and averaged. The index finger was rapidly moved, held in position, and returned only after analysis time. Four to five hundred finger movements at irregular intervals of 4-5 sec were averaged per experiment. Subjects fixed their gaze on a given spot during trials and avoided eye blinking. In addition, oculomotor and other artifacts were eliminated by a preaverage editing procedure. Beckman Ag/AgC1 electrodes were affixed to locations C′3, C′4 (defined in Deecke et al. 1969), Cz, P3, P4, and Pz (10/20 system) and referred to linked earlobes. Monopolar recordings and two bipolar derivations (C′3-C′4 and C′3-Cz) were stored on tape and reverse-averaged off-line. BP amplitude was calculated as the arithmetic mean of the six monopolar leads (five leads in group I because there was no vertex recording). Two points of measurement were selected: BPo = amplitude (with respect to a pre-potential base line) at the first EMG activity, and BP150 = amplitude 150 msec prior to first EMG activity. Statistical analysis included an analysis of variance and correlation tests.

Results

BP amplitude was found to be relatively constant until the end of the fourth decade (39 years) after which the amplitude gradually declines. In Fig. 1, typical examples are given of the cerebral potentials preceding voluntary finger movement. In a group II subject (left), aged 31 years, all three potentials are clearly discernible (right-sided movement): (1) the BP in all monopolar recordings, with a maximum at the vertex; (2) the premotion positivity (PMP) in all monopolar recordings with a maximum midparietally; and (3) the motor potential (MP) in the bipolar recordings C′3 versus C′4 and C′3 versus Cz. In the C′3-C′4 derivation, a slight contralateral preponderance starts about 300 msec prior to the onset of EMG activity (0). In a group III subject (right), the BP recorded under similar conditions was smaller. Its amplitude further decreased with older age groups. Above 60 years positive BPs occurred occasionally in all monopolar recordings (Fig. 2). In younger adults, positive BPs are found only in frontal leads.

In Fig. 3, the mean BP150 (hatched) and BPo (white) amplitudes of the different age groups are shown. A gradual decline of the two BP amplitudes is seen. The analysis of variance of BP150 for groups II to V was marginally significant (F=2.9, p=.06). The analysis of variance of BPo was significant (F = 5.1, $p < .01$). The slightly larger BPo amplitude in group II, as compared to I, can be explained by the missing vertex recording in group I.

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[1] Supported by the Deutsche Forschungsgemeinschaft, SFB 70.

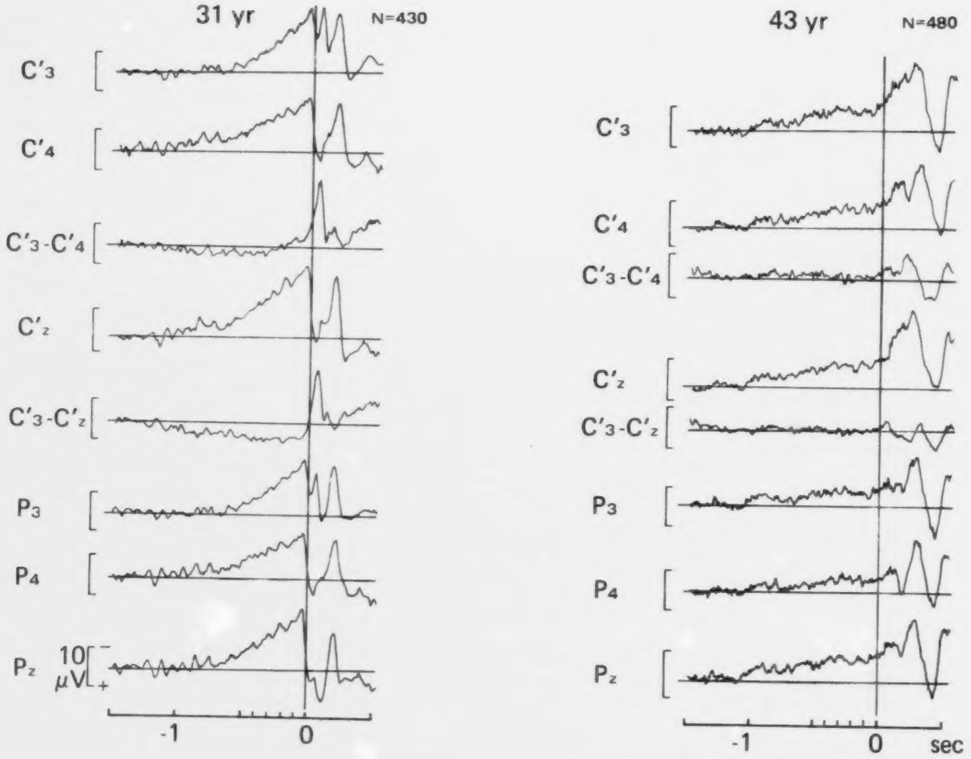

Fig. 1. Typical examples of movement-related potentials at different ages. Cortical activity preceding right-sided voluntary finger movement in a 31-year-old subject (left) and in a 43-year-old subject (right). The vertical line represents EMG onset. In the left column, three potentials are clearly discernible: (1) the slow negativity of the BP, starting 1 sec before EMG onset and maximum at the vertex; (2) premotion positivity, starting about 80 msec prior to EMG onset, maximum midparietally; and (3) the motor potential as additional negativity over the motor cortex about 60 msec prior to EMG onset, typically seen in the bipolar recordings C'3 vs. C'4 and C'3 vs. Cz. In the 43-year-old subject at right, the BP is markedly smaller. N, number of trials.

A significant negative correlation was found between BP amplitude (averaged from all six monopolar leads in each subject) and age. The correlation coefficient (r) for BP150 was 0.58 (2p $< .01$); the correlation coefficient for BPo was 0.66 (2p $< .001$).[2] Correlations, like analysis of variance, were computed only on the data from groups II to V ranging from 30 to 69 years of age.

Fig. 4 shows the regression lines at the different electrode locations, as indicated for BPo (solid lines) on the left, and for BP150 (dotted lines) on the right. All correlations were significant on the basis of the two-tailed hypothesis, except for BP150 at P3 matching only the one-tailed test.

Unlike the BP, the regression line for the MP (estimated as the difference BPo - BP150 in a bipolar recording, C'3 versus C'4, cf. Deecke et al. 1969, 1976) was not significant (coefficient of determination r^2 = 0.066). This finding indicated that the motor potential, which reflects the activity in the contralateral motor cortex immediately prior to the onset of EMG activity, is relatively constant with age.

Discussion

A gradual decline with age of the average BP amplitude after the fourth decade of life is documented here. The reduction of BP as a result of aging is probably a true diminution of this cortical potential. It seems unlikely that the reduction is solely caused by an increase in skull thickness or in the amount of cerebral spinal fluid between the cortical surface and the skull. Such factors would affect other potentials as well, and the amplitude of the alpha rhythm, for instance, is not markedly reduced with age. Also, the fact that the motor potential was found not to be significantly affected by aging (Fig. 4) is not consistent with the assumption of a general reduction of all cortical potentials with age. Late components of

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[2] Two-tailed test.

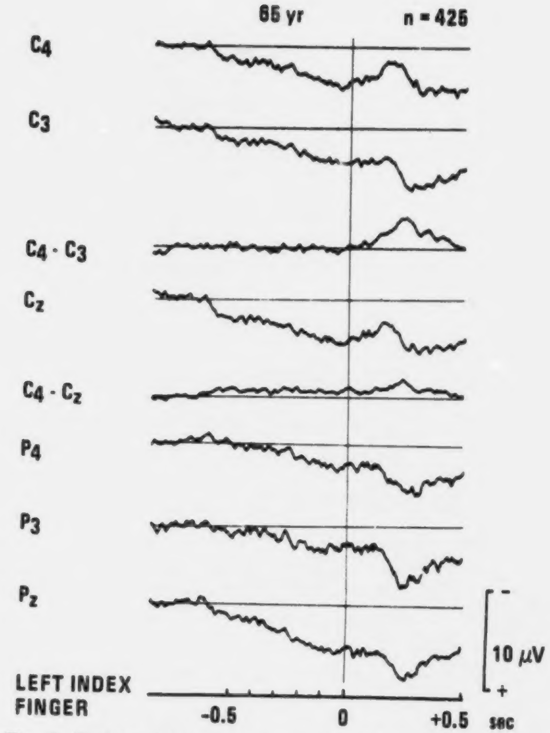

Fig. 2. Positive BP in a 65-year-old subject. C'4, C'3, Cz, P4, P3, and Pz electrodes were referred to linked earlobes. The subject performed 425 left-sided finger movements, but positivity occurred also with right-sided movements.

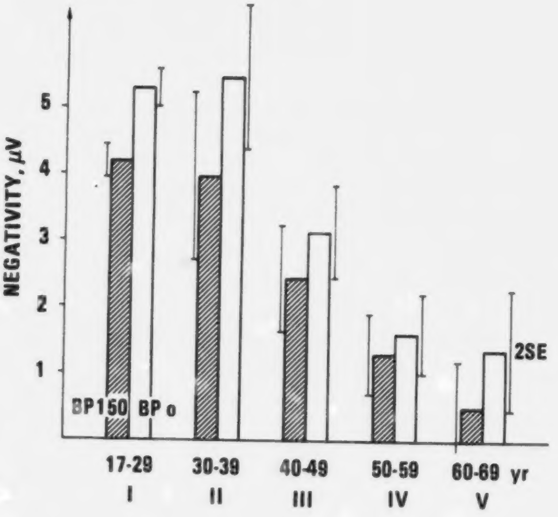

Fig. 3. Mean BP amplitudes in the different age groups. Blank columns: BP amplitude at movement onset (first EMG activity); hatched columns: BP amplitude 150 msec prior to EMG onset. Group I (17-29 years) consisted of 34 previous experiments (therefore smaller standard errors, SE, than in groups II to V). Groups II to V consisted of six subjects each.

average evoked responses and the CNV have been reported by some authors to be reduced with age, while others found little or no reduction in amplitude, if a certain level of motivation was maintained (Marsh 1975, Lüders 1970, Loveless and Sanford 1974). The factors responsible for the age-dependent BP reduction are not yet known, but among others a general decrease in motivation as well as the rarefaction of cortical elements have to be considered. In senile dementia, the late components of the visual evoked response are even increased (Visser et al. 1976).

The observation of occasional positive BPs in the older age group (60-69 years) is difficult to explain. In younger adults, positive BPs only occur over the frontal region referred to either linked ears or mastoids (Deecke et al. 1969). In patients with bilateral Parkinsonism, an all-positive BP is often found (Deecke et al. 1977). The present results show that it can also occur in healthy elderly subjects, although the significance of this finding is not clear. Karrer et al. (this section and personal communication) reported positive BPs in mentally retarded children. Since mastoid or ear references have been used in BP studies of the elderly and the retarded, observed positivity could result either from absolute positivity over the convexity of the skull, or from greater negativity at the reference electrodes, which reflect activity from temporobasal cortical structures.

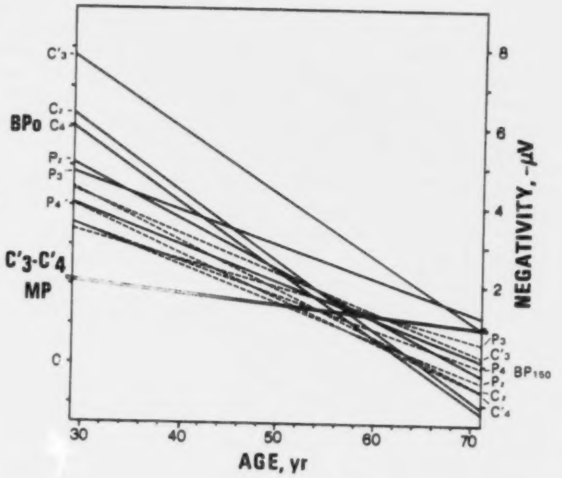

Fig. 4. Regression lines at the different recording locations. Solid regression lines for BPo with electrode locations indicated on the left; dotted regression lines for BP150 with electrode position indicated on the right. For simplicity, subscript 3 stands for contralateral electrode positions, subscript 4 for ipsilateral locations for left-sided movements as well as for right-sided movements. Double regression lines for the motor potential (MP), measured as the difference BPo - BP150 in a bipolar recording contralateral versus ipsilateral precentral (cf. Deecke et al. 1969, 1976).

AGING EFFECTS ON THE HUMAN EVOKED POTENTIAL[1]

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In the quest for understanding how aging affects brain mechanisms, the averaged evoked potential (EP) has been an effective tool. The reverse may also prove to be the case–that aging effects may prove to be useful tools in understanding mechanisms underlying the generation of EPs. The following review is intended to show how EPs have been used in studying the effects of aging and to note how changes seen in EPs may be related to changes in physiology and anatomy.

Passive stimulation

Contrasting EPs from young, mature subjects with EPs from older subjects has shown the early components (20-80 msec latency) to be larger in the older group. Shagass and Schwartz (1965a) measured somatosensory (S) EPs from electrodes placed on a parasagittal line 7 cm left of the midline with the "active" electrode 2 cm posterior to a line from vertex to the auditory meatus and a "reference" electrode 6 cm anterior. Peaks falling at about 20-, 40-, 50- and 80-msec latencies were smallest in amplitude in a 20- to 39-year-old age group and were increasingly larger in two groups, 40-59 and 60-80 years of age. The latency of the peaks at 20 and 40 msec was found to be longer in the older groups. One set of positive-negative peaks at about 30 msec was omitted from analysis since they were not found in the oldest two groups. Peaks falling at longer latencies were not explored.

Lüders (1970) recorded SEPs from the same sites as Shagass and Schwartz (1965a), but against an ipsilateral ear reference. He measured SEPs in four different age groups (X = 23.6, 36.4, 51.6, 62.0) and found somewhat similar changes in amplitude, but opposite changes in latency. A peak falling at about 25 msec increased in amplitude, and a succeeding peak at about 30 msec decreased in latency across age groups (45-70). Peaks falling at about 50, 70, and 110 msec increased in both amplitude and latency with age (again, past 45 years). Later peaks falling at approximately 250 and 400 msec decreased in amplitude as early as 30 years of age and remained relatively unchanged with age thereafter. These later peaks also showed no changes in latency across age groups.

Schenkenberg (1970) was unable to replicate either the increased amplitude or longer latency of early components when recording from C3 and C4 to linked earlobes. Instead, a marked decrease in amplitude was found for some late components (100-200 msec) after the teenage years and a rather remarkable stability was found for the early components. The latencies to peaks were found to be increased for some of the early and all of the late components. Since many of the early SEP components are only seen contralateral to the stimulated limb, the above measures pertain only to contralateral measures. However, those components that could be measured on the ipsilateral hemisphere showed similar changes.

Shagass (1968, 1972) has also presented data on EP "recovery." In this paradigm, an initial stimulus is given, and then a second identical stimulus is presented after some short, fixed delay. The EP to this double stimulation is obtained, and then usually the EPs to single stimuli are subtracted so that a "residual" EP elicited by the delayed stimulus is obtained. Such EPs show greater amplitude with shorter delays for older subjects at peaks falling at 20, 30, 40 and 80 msec. The latency of these peaks is delayed, however, and does not recover at as short an interstimulus interval in the older subject as it does in the young. This delay was found at peaks with the following latencies: 32, 35, 40, 45, 50, 80, and 110 msec.

There has been only one investigation of aging effects on the auditory (A) EP. Schenkenberg (1970), recording at C3 and C4, found no changes in the components of the AEP from the late teenage years through old age.

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[1] This work was supported in part by training grant AG 00017 and research grant AG 00364 from the National Institute of Aging.

More studies have been carried out on the visual (V) EP. One early study (Shagass et al. 1965) reported no age differences during the first 200 msec from an Oz -Cz derivation. The age range, however, was from 19-45. Studies extending further into old age with careful attention to sex differences have shown a number of age-related differences. Straumanis et al. (1969) found that a group of subjects with an average age of about 70 had greater amplitude components at 30-, 40-, and 90-msec latencies and were longer in latency on the first six of eight components measured when compared to a younger group (19-45 years, average 24 years). These EPs were obtained from a midline site approximately at Oz and referenced to a midline electrode 12 cm anterior.

Kooi and Bagchi (1964) recorded EPs from midline occipital, parietal, and central locations against a linked ear reference and found similar data. The age range of their population (N = 130) extended from 28 to 72 years, with only six females in the group. They found a peak-to-peak measurement of components in the 80- to 90-msec latency range to correlate at a low ($r = 0.21$) but significant level ($p < .05$) with age. The latency of a wave occurring with a latency of about 70 msec was also positively correlated with age at a low ($r = 0.26$) but significant level ($p < .05$). They could, however, show no relationship of a later wave (latency about 140 msec) to age. They also reported no relationship between pupil size and EP amplitude or latency.

Dustman and Beck (1966, 1969) using subjects over a wide age range, reported similarly that early components (before 100 msec) of the VEP recorded from 01 and 02 (to linked earlobes) increased in amplitude from age 20 to 30 years. Peaks occurring later, especially after 200 msec, decreased markedly in amplitude after the teenage years. The same pattern was reported by Schenkenberg (1970), who found all peaks increased in latency starting in middle age. Some acceleration of the amplitude loss was seen in old age for the latest peaks, about 300 msec. Similar trends were observed for frontal (F3 and F4) and central (C3 and C4) recording sites, with one exception. Central sites showed an increase in amplitude of a component occurring at about 100 msec.

Schenkenberg also used a cumulative voltage measure to analyze the amount of deviation from baseline over set intervals (e.g., 0-100, 101-200, 202-300, and 302-600 msec). These values showed the same trend for all modalities and all recording sites—an increase in voltage deviation in the post-300-msec range, starting at about age 40. Some increases were noted in earlier components, usually in the primary region for that modality and in the frontal region.

A notable exception was the VEP recorded from 01 and 02 where cumulative voltage decreased sharply after age 40. In this case, voltage diminished over primary visual areas, but increased over the central region in older subjects. The cumulative voltage measure in the post-primary time period may, therefore, reflect alpha-like after-discharge in the visual modality.

Changes in cumulative voltage, in general, paralleled changes in EP components occurring within the same time intervals. In the late (post-300-msec) interval, there often were no specific EP components against which to compare this activity. The extent to which differences between cumulative voltage and peak-to-peak measures are indicative of brain aging remains to be determined.

Buchsbaum et al. (1974b) also reported a decrease in VEP for peaks falling between 100 and 200 msec in male subjects. These VEPs were recorded from the vertex rather than occipital area. Notably, they found that older subjects had considerably greater stability in VEP amplitude as the stimulus varied over four different intensities. Conversely, these investigators observed less stability over replications in the auditory EP of subjects over 40—especially in the longer latency peaks (beyond 256 msec).

A light source with intensity modulated by a continuous sine wave function can be used to elicit a sine wave-like EP. Age-related changes in the phase lag between stimulus and EP peaks have been studied (Perry and Childers 1969). In the stimulus frequency range of 12-30 Hz, the average subject under 45 years of age demonstrates a latency of 77 msec, while older subjects have an average latency of 102 msec.

Another variable that needs to be considered is the subject's sex. Most reports of aging effects on EPs have dealt almost exclusively with male subjects. Shagass and Schwartz (1965 a,b) and Schenkenberg (1970), however, have shown that older women have higher amplitudes and shorter latencies than men in most EP components for all modalities. These effects could result from hormonal differences, although this explanation seems less likely as females exhibit the same or even larger differences after menopause. Buchsbaum et al. (1974b) have reported higher amplitudes and shorter latencies in visual EPs of children before puberty, although Schenkenberg (1970) found the reverse: larger VEPs in males than females before adolescence. Evidence for any mechanism other than CNS responsivity to gonadal hormones is lacking at the present time.

Cognitive influences: CNV and the late components of the EP

Despite the diminishing amplitude with increased age reported for late EP components under passive stimulation conditions, the same loss of amplitude is not as marked when the subject must deal cognitively with stimuli. Marsh and Thompson (1972) found that late components of auditory EP of young and old groups did not differ when subjects were judging stimuli for slight differences in pitch. Schenkenberg (1970), however, has reported that AEPs were less sensitive than VEPs to age differences.

Marsh (1975) has demonstrated VEP differences between young and old. The task required searching a mental list to ascertain if a low-intensity illuminated digit, presented at the fixation point, matched any of the mentally stored digits. The average amplitude of the late positive component of the older group was smaller than that of the young group at Cz, Pz, and C6. No difference was found at Fz or C5. No difference in latency for this late component was found between groups.

A study of CNV amplitude in a task in which the pitch of tone pips was being judged showed no difference between the old and the young (Marsh and Thompson 1973). Loveless and Sanford (1974), in a study employing long intervals (up to 15 sec), found the elderly lower in CNV amplitude when performing in the usual fixed foreperiod RT tasks. The older group, however, did not differ from the young when irregular foreperiods were used. The authors noted that the waveform appeared to have two components, an early negative "orientation" wave at about 1 sec and a later negative CNV response shortly before the imperative stimulus. The young group, in particular, showed a sudden increase in CNV just before the imperative stimulus. Such activity might have resulted from motor readiness potential activity. Since reaction times were longer in the older group, especially at the longer intervals, readiness potentials would not have been as likely to appear in the old group during the "CNV interval." Deecke et al. (this section), however, reported decreasing Bereitschaftspotential with increasing age past 40 and almost no potentials in subjects over 60 years, findings which could also account for lower amplitudes at long foreperiods as observed by Loveless and Sanford (1974). Moreover, the latter authors reported that, about 1 sec after the warning signal, "orientation" potentials appeared which were larger in the younger group. Further attention should be given to this phenomenon since other work has often confused this earlier waveform with the final level of the CNV.

Thompson and Nowlin (1973) found age differences in RT, but only marginal differences in CNV amplitude between an old and young group. The young group demonstrated increased CNV amplitude and slowed heart rate on fast RT trials. The older group did not demonstrate this concordance of response. Froehling (1974) was able to show a correlation among CNV amplitude, heart rate, and reaction time in an older group of males. Her subjects, however, were especially chosen to be in excellent health and were also well practiced on the task (for several days). By far the strongest relationship was between CNV amplitude and RT, with heart rate and heart rate x CNV amplitude being weak predictors.

Anatomical and physiological correlates

That the body undergoes change with increasing age has never been disputed. The difficulty has been to ascertain those changes resulting from disease or accident not directly applicable to the study of aging. The loss of neurons in certain parts of the neocortex with age was shown many years ago (Brody 1955). This has been more finely detailed in recent years (Brody 1973) to show the greatest loss in layers 2 and 4. Since these layers have neurons with inhibitory effects on underlying neurons, this finding could be interpreted to support the observed increase in early EP components. Furthermore, Scheibel et al. (1975) have demonstrated a marked decrease in the number of dendrites and dendritic spines with age, evidence that may be related to the reduction of amplitude in late EP components.

CNS reactivity is also controlled to some extent by hormonal influences. Changes with age in how the body handles major hormones are now being uncovered. Such alterations could produce positive feedback, triggering cascading effects throughout the body (Finch 1973). Ten years ago theories of aging changes in the CNS emphasized ischemic or anoxic effects of reduced blood flow. Such effects, however, can no longer be seen as the sole mechanism behind changes in the aging brain. The interface between neurochemistry and psychophysiology in the gerontology of the CNS could be fruitful over the next decade.

Conclusion

The evidence reviewed here suggests that the CNS continues to change throughout the life cycle. Changes in various EP parameters have been observed across the life span, although the mechanisms underlying these changes are not understood. Animal models for studying the neurophysiology of aging are problematic. Since primates are long-lived, old animals are difficult to obtain. On the other hand, short-lived species, such as the rat, are too remote from man on the phylogenetic scale to provide an effective model for human aging processes. Therefore, *homo sapiens* appears to be the best "model" for such studies!

Experimental psychologists have provided a number of profitable routes of attack on the perceptual and cognitive changes with age (Birren and Schaie 1976). This body of knowledge may enable psychophysiologists to act as synthesizers between psychology and physiology. The use of pharmacologic intervention may allow the testing of proposed physiologic mechanisms in man. Even without the use of drugs, if some cognitive processes are slowed with age, then parameters of the EP associated with such processes should demonstrate such slowing. It may be possible to tease apart EP components that overlap in younger subjects but are separated in latency with increasing age.

One of the difficulties in research on aging population is to separate the effects of disease, which appear more frequently in older age groups, from the effects of aging *per se*. The matter of healthiness is always one of degree, but can be crucial when subjects from old-age groups are used, as noted in the Froehling (1974) study. A balanced emphasis on health, cognitive and perceptual factors, and physiological mechanisms should lead to a useful role for psychophysiology in the study of aging processes.

DEVELOPMENT AND DEVELOPMENTAL DISORDERS: DISCUSSION SUMMARY[1]

Harter questioned how one can meaningfully interpret ERP changes during a task unless performance in the task is directly assessed. The question is further complicated if a clinical population is used, subjects who may not cooperate or follow instructions, as well as those who are normal. The question becomes: What happens to ERP differences between normals and abnormals when performance on a task is directly measured or matched? *Knott* argued for standards against which to assess brain activity.

Harter felt that the presence or absence of components P2 and P4 might have considerable clinical importance. A lack of change in P4 to check size might indicate that the cortex of the infant older than 3 months was not developing normally. *Knott* asked if *Harter's* data were due to maturation changes in the optic tract, the retinal system, or the geniculate. It is important to try to get an idea of just where these changes occur. *Knott* also encouraged the analysis of the motor potential in the young child. Many techniques now used in infant research, such as an operant conditioning paradigm, could be fruitfully applied in ERP research.

Marsh stressed that aging provides a natural experiment that begins at birth and ends at death. Viewed in this light, the life span constitutes a continuum in which the brain is changing in ways that we are beginning to understand.

Knott asked if experimental manipulations of the normal subject that mimic the abnormal could provide clues for changing the abnormal to normal. *Fenelon* answered that it was uncertain how far that model could go but that it was necessary to pursue it.

Fenelon stated that his studies with dyslexics by means of spectral analysis confirmed work done elsewhere, i.e., greater activity in theta and beta bands and less in the alpha range during rest. Overall, the energy output for dyslexic children is considerably lower. The evoked responses are lower in amplitude than in normal subjects and have less lateral asymmetry. It is uncertain if these data reflect lesions, problems in interhemispheric transfer, or developmental lags in critical areas of the brain such as the secondary posterior association area in the left hemisphere. *Fenelon* further stated that the clinical objective of ERP research must be prescriptive treatment rather than diagnosis or prognosis alone. We already know who the problem children are. CNS measures or evoked response measures should provide clues on how to tailor procedures for individuals, perhaps feedback procedures or some special sensory input coupled with lateralization. *Fenelon* felt that *John's* procedures would go far in this direction.

Stamm, noting that Arthur Rubenstein still played the piano well at 87, asked *Deecke* about the significance of the decline in the Bereitschaftspotential (BP) in the elderly. *Stamm* wanted to know whether there is any relationship to motivational factors or to response characteristics. *Deecke* replied that it is very difficult and dangerous to say that motivation is affected by age, that older subjects have less motivation. The diminution is a matter of differences in performance. BP amplitude was larger preceding slow movement than rapid movement and, therefore, was related to response characteristics. *Knott* felt that motivation can obviously be affected by age and that one needs to establish some standard for motivation.

Dongier reported studies on BPs in depressed patients in his laboratory that showed no amplitude effects. In subcortical recordings in Parkinsonian patients, there was a positivity preceding the onset of EMG in an area rostral to the thumbs in a voluntary motor task. He wondered if the Bristol group had observed this phenomenon also. *Dongier* also pointed out that BP will be larger if there is some outcome. Simple finger flexions give relatively small BPs. It may be that as one gets older, one becomes more bored with just flexing one's finger 400 times.

Deecke thought that *Dongier's* recording of negativity on the cortical surface (or scalp), positivity in the white matter, and negativity again in the thalamus could be understood in terms of volume conduction, i.e., a sink in the white matter. *McCallum* thought that one would see a possible positive effect in the caudate nucleus.

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[1] Editor's note: This summary was prepared by Dr. Karrer from the transcript of EPIC IV discussions related to developmental issues and the foregoing papers. The discussion and papers were originally part of the Psychopathology plenary session.

Rosen wondered if structural changes in the skull, which occur with age, such as calcification of bony structures, or thickening of membranes, affect BP via increased resistance or passive effects. *Deecke* responded that, if this were so, not only BP but all other potentials likewise should be diminished. This was not the case; i.e., the motor potential was less affected than the BP and there was no reduction in alpha activity. Therefore, the selectiveness of the reduction cannot be explained in that way.

Otto pointed out that *Grant* (this volume) presented a schematic diagram of "functional brain capacity" that corresponded well to the changes observed by *Karrer* in children and by Deecke in the elderly.

Otto recalled that *Loveless* used a very long foreperiod and found an interesting phenomenon. In younger adults, there was no sign of negativity until very close to the point where the onset of movement should be, where the BP occurs associated with the movement. But in older adults, there was not much negativity, unless there was perhaps a long sustained (baseline) negativity. The old adults appeared to be having trouble gauging the time period so that the late negativity seen in younger adults was not seen. There was a great difference in the ability to prepare. *Knott* felt that this issue should be further explored with appropriate experimental designs. *Loveless* (in a comment submitted after the conference) stated that, while he was convinced that the E wave of his data was a BP, he was not certain that *Deecke's* data would explain the elderly's poor RT with long predictable foreperiods. The obvious possibility is that the elderly show a BP at short foreperiods, but not at long ones.

Teece said that the fact there is a dissociation in the aged on hard/easy items on the Wechsler memory scale and other kinds of tests, particularly tests involving short-term memory and distraction, suggests that there is more to the poor performance problem than just motivation. With praxolone, a vasodilator, it is possible to increase the capacity of the aged to do better on some of these memory items. It would be of interest to see what sort of effects could be obtained with the BP. To *Tecce* it is clearly not just motivation because the aged can do as well as the young on the task. *Deecke* injected the comment that there has been a paucity of pharmacological studies of BP. One should first establish the response of the normal and the younger subjects and then go on to older populations.

Deecke commented that, in *Karrer's* data, positivity was early and that he (*Deecke*) has also found such curves in the evoked potential but did not schematically indicate it. *Deecke* did not know what it was—perhaps a different distribution of negativity. Perhaps the negativity first arrives at the convexity and then is more involved with basal structures. He also commented on *Karrer's* recording of EMG from the opposite, nonresponding thumb. Certain cerebral palsied patients are unable to make a unilateral movement; unilateral efforts in these patients are always accompanied with similar movements on the other side. Shibasaki and Kato (1975) studied this phenomenon in normals by comparing the BP during unilateral and bilateral movements. They proposed that any unilateral movement is actually a unilaterally inhibited bilateral movement.

Karrer responded that motor overflow and the development of inhibition of overflow in children is a clinical sign commonly used by pediatric neurologists. Even on simple movements, some overflow is present. The more complex the motor path, the more overflow is present, a disparity that is inversely related to age. Individuals differ in the ability to inhibit extraneous movement, especially across the midline, even in adulthood. The complexity of the positive-negative-positive BP observed by *Karrer* in children might be related to extraneous movements occurring simultaneously. Motor response patterns and the inhibition of extraneous movements are poorly differentiated in children. To obtain data relevant to that problem, he recorded the thumb contralaterally and also saved those trials that had a coincident eyeblink within a defined time window at thumb press to see if simultaneous extraneous motor responses make a difference in waveform or amplitude.

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VI. PSYCHOPATHOLOGY

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EVENT-RELATED POTENTIALS AND PSYCHOPATHOLOGY[1,2]

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In 1966 Grey Walter commented that studies of intrinsic electrical activity of the human brain have contributed little to an understanding of either psychopathologic processes or clinical diagnosis (Walter 1966). In his opinion, event-related brain potentials including the contingent negative variation (CNV), held more promise.

In pre-Congress (EPIC IV) correspondence among members of this panel, Knott raised the question: "Why is slow potential research in psychiatry unproductive?" His question evoked a flurry of defensive responses, but it became obvious that investigators of event-related potentials and behavior (normal or pathologic) have concentrated, often exclusively, on one of four types of ERPs (Fig. 1). Some study early or late potentials; others study surface negative or positive activity. In effect, many ERP investigators develop a self-limiting type of visual field defect. One group has a right homonymous hemianopsia and sees only early processes. Another has a left-field defect and sees only late processes. Some have further combined defects: upper field, who perhaps see only late positivity, or lower field defect, who see only late negativity. Development of such types of blindness impedes achievement of a fuller understanding of event-related

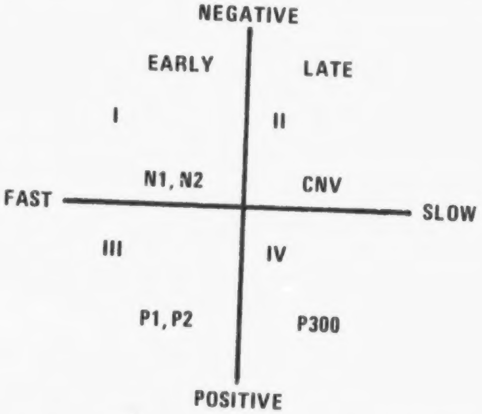

Fig. 1. Four classes of event-related brain potentials based on polarity at recording site and early versus late occurrence.

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[1] *Panel participants*: John R. Knott and Joseph J. Tecce, Co-chairmen; Peter Abraham; Enoch Callaway; Maurice Dongier; Bernardo Dubrovsky; Gilbert Lelord; Martine Timsit-Berthier; Roberto Zappoli.

[2] The chairmen note that another review of CNV, other late slow potentials, and psychopathology, which has borrowed quite heavily from this panel's EPIC IV precirculated material, pre-Congress correspondence and Congress presentations, has been presented elsewhere (Roth 1977).

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potentials and their relation to behavior, and limits productivity in the area of psychopathology.

Pre-Congress correspondence also indicated the need to discuss five particular topics if the central question were eventually to be resolved. These included:

1. Subject populations and relations between ERPs in normal and pathologic groups. Pathology itself is in need of rigorous operational definition for proper classification of subject populations.
2. Procedures. Basic methodology must be established for eliciting and scoring ERPs and manipulating them by pharmacologic and other parameters.
3. Response measures. Such critical terms as CNV, PINV and P300 must be defined operationally and logical methods determined for interrelating these and early potentials (N2, P2, etc.). Response measures such as breathing and EKG should be correlated with ERPs.
4. Usefulness of explanatory hypotheses. In particular, the ceiling hypothesis (Knott and Irwin 1967, 1973), distraction-arousal hypothesis (Tecce et al. 1976), the concept of an inverse relationship between stress and CNV magnitude (Knott and Irwin 1973), and possibly shape (Tecce 1972, van Veen et al. 1973) should be evaluated.
5. Electrogenesis. Especially as deduced from topographic distribution of ERPs in relation to pathology and to task set, a more rigorous investigation of electrogenesis should be profitable.

Each of these areas should be attacked through studies of normative as well as psychopathologic material. Indeed, we were of the opinion that experimental analogs of psychopathology could be established in presumably normal subjects. Such analogs could include the use of psychotropic drugs (how else can the effect of drugs upon psychiatric patients be understood?) as well as manipulation of tasks or external stimulating conditions. Delaunoy and his colleagues (this section), in fact, describe a simple method to induce PINVs in normal adults. Attempts to create such models may help us to understand the mechanisms that produce abnormal ERPs in psychopathologic states and to discover methods for reversing both the effect and the cause.

Returning to Fig. 1, and the classification of ERPs, the newly developing area of "far-field potentials" (Jewett et al. 1970) will require further incorporation into the full matrix of CNV data processing. These events, which occur within 10 msec of stimulus onset, appear to yield clinically useful information about brain stem integrity. Although they may not relate as dependent variables to attentional or behavioral variables, they may serve as indices of independent variables subserving such processes. Since far-field potentials indicate the intactness of sensory pathways preceding higher processing, the applied investigator may be able to utilize brainstem EPs in assessing the environmental insults that induce neuropathy. (See Seppalainen, this volume.)

One may be critical of the fractionation of efforts by ERP investigators with upper- and lower-field defects who study either CNV or P300 and ignore the opportunity to experimentally manipulate (possibly simultaneously) both the slow negativity (CNV) and the late positivity (P300). A combined approach would help us understand what each may signify in terms of psychophysiological correlates. Upon this groundwork were laid the discussions that took place during EPIC IV.

* * *

The section of "Psychopathology" was opened by *Tecce*, who summarized experimental and clinical studies being conducted with his colleagues at Boston State Hospital. The experimental work involved the alteration of CNV development by two environmental challenges, distraction and drugs. The clinical research included the change in CNV development in schizophrenics and former heroin addicts by drug therapy, and alterations of CNV development in the aged. He described disruption in CNV development in the aged as reduced amplitude associated with lengthened (slower) reaction time to S2 during short-term memory tasks and termed this a "CNV distraction effect" (Tecce et al., this volume). Associated increases in heart and eyeblink rates were considered evidence of elevated levels of arousal. Four measures showed reliable changes: CNV (decrease), reaction time (increase), heart rate (increase), and eyeblink rate (increase) during sustained distraction (continuous mental arithmetic) and during both visual and auditory phasic distraction. These four measures were viewed as reflecting a distraction-arousal coupling and as indexing an experimental analog of psychopathology. He then presented the distraction-arousal hypothesis (Fig. 2) to explain psychopathology, particularly in schizophrenics (Tecce and Cole 1976). He also showed that CNV prolongation of the type ascribed to schizophrenics (see later discussions by Dubrovsky, Dongier and Timsit-Berthier) can occur in a normal individual in the state produced by distraction-arousal (Fig. 3) and inferred that post-imperative negative variation (PINV) may be a reflection of distraction-arousal coupling in schizophrenics (Tecce and Hamilton 1973).

Tecce pointed out that, although eyeblinks are usually regarded as an undesirable artifact, they may well be a sensitive and accurate indicator of disturbed psychological functioning. (See Tecce et al. 1978).

He also reported a CNV rebound phenomenom that was unexpectedly found in a study of short-term

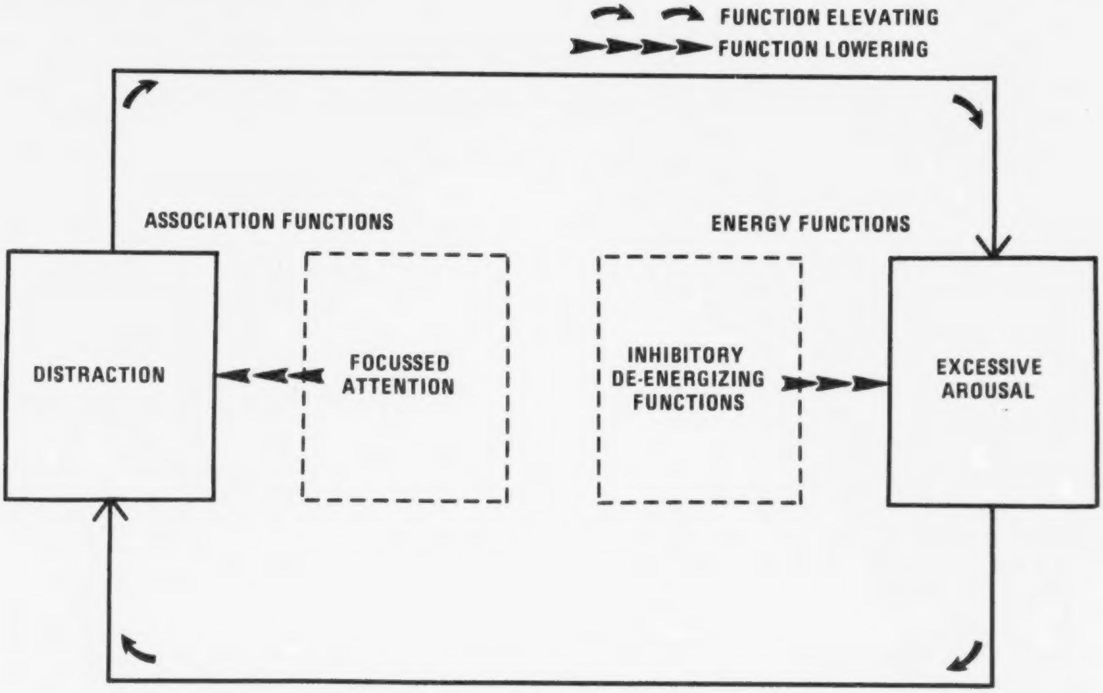

Fig. 2. Schematic diagram of a model showing a distraction-arousal association and interrelationships among attention, arousal, and distraction processes. Distraction normally elevates arousal levels. Focussed and narrowed attention, by reducing distraction, can attenuate excessive arousal. Excessive arousal levels heighten distractibility and, therefore, increase the likelihood of distraction. Inhibitory functions, such as those produced by neuroleptic drugs, reduce distraction by decreasing excessive arousal levels. Reprinted from Tecce and Cole (1976) by courtesy of author and Prentice-Hall.

memory effects on CNVs of 36 normal volunteers. In this experiment, the control condition consisted of light, tone, key-press trials, and the distraction task consisted of two types of randomly mixed trials, (1) those identical with the control condition (no-letter trials) and (2) those with auditory letters presented within the light tone (S1-S2) interval for short-term memory (letter trials). The reliable and expected CNV decrease was found for letter trials, but an unexpected CNV increase above control CNVs was found for no-letter trials. The enhancement in CNV amplitude in no-letter trials above values found in control trials is approximately equal in magnitude to the reduction in CNV amplitude in letter trials compared to control trials. This rebound effect is absent in elderly individuals and patients subjected to prefrontal leucotonmy and, therefore, may be an indicator of plasticity of brain functioning.

Tecce also reviewed data on the influence of psychotropic drugs on CNV development in normal and clinical populations. CNV amplitude was an accurate indicator of early paradoxical drowsiness and later alertness and excitation produced by dextroamphetamine in normal volunteers. Individuals characterized by basal CNV shapes with a slow rise time (Type B) typically showed the paradoxical drowsiness (and, in some cases, increases in dysphoric mood), but individuals having basal CNV shapes with a fast rise time (Type A) did not (Tecce and Cole 1974). Phenobarbital tended to produce greater dysphoria and CNV disruption in Type B than in Type A subjects (Tecce et al. 1977), and former heroin addicts having Type B basal CNVs tended to become less agitated when given methadone and showed increased CNV amplitudes compared to Type A patients (Tecce et al.,in press). Evaluation of drug effects on ERPs and clinical state in chronic schizophrenics indicated increases in CNV amplitude and clinical improvement following chronic administration of mesoridazine and thioridazine (Tecce et al. 1978) and decreases in CNV amplitude and clinical deterioration in patients receiving fluphenazine enanthate and decanoate (Tecce and Cole 1976).

Finally, in a study of the effects of psychosurgery carried out for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, it was found that amplitude of CNV recorded at Cz and Pz tended to be higher in patients

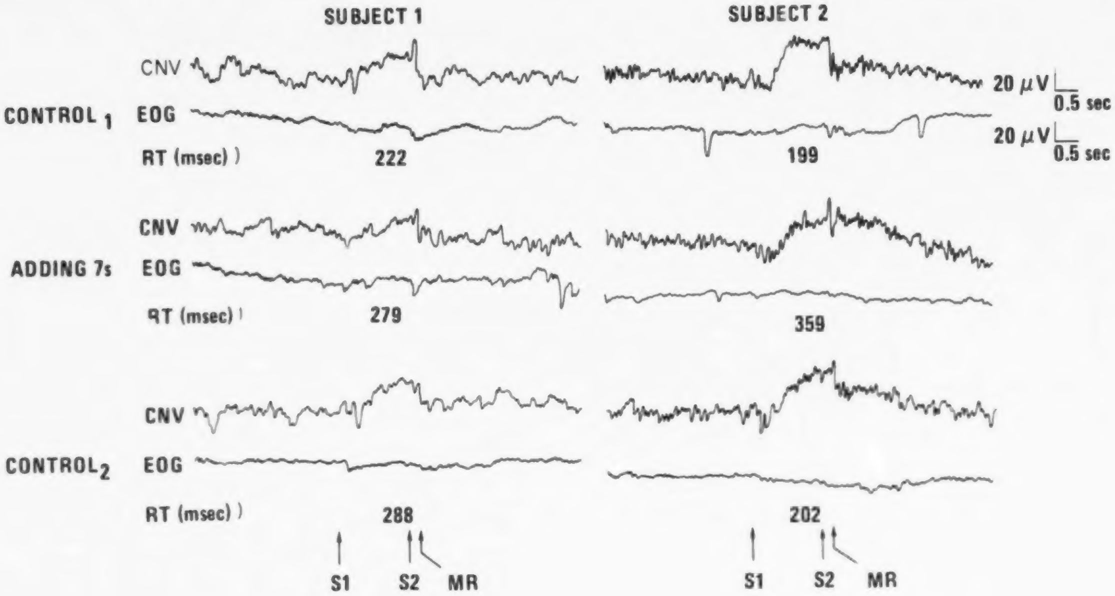

Fig. 3. Example of CNV reduction during sustained distraction produced by sustained cognitive activity (adding sevens) in two young normal subjects. For subject 2, distraction produced CNV prolongation accompanied by lengthened reaction time to S2 and elevated levels of heart rate and eyeblink rate (distraction-arousal coupling). The occurrence of similar CNV prolongations in schizophrenics may also reflect distraction-arousal processes. CNV (six trials per average) was recorded from vertex (Cz) and linked mastoid processes. EOG was recorded from above and below the right eye. Relative negativity at Cz and the supra-orbital site is upward. Reprinted from Tecce and Hamilton (1973) by courtesy of author and Elsevier Publishing Company.

having a more favorable outcome than for those having a less favorable outcome (Tecce 1977). (Eyeblink frequency was the most sensitive measure differentiating the two groups: the less favorable outcome group blinked 35 times per minute compared to 25 times per minute for the more favorable outcome group.) The one CNV deficit in the more favorable outcome group was a reduction in frontal CNV, presumably an indication of the cognitive cost these patients paid for the amelioration of their emotional disturbance.

On the basis of these experiments, Tecce concluded that (1) distraction is a reliable source of CNV disruption and impairment in reaction time performance, (2) distraction-arousal coupling is useful in studying ERPs and psychopathology, (3) eyeblink frequency is a useful adjunct indicator of disturbed psychological functioning, and (4) Type A and B CNV shapes may be useful predictors of the therapeutic effectiveness of psychotropic drugs.

While these experiments demonstrate that models of "abnormality" can be created by environmental manipulation of normal subjects, *Knott* believed that distraction is a type of stress induced by the need to perform simultaneously conflicting tasks. Because the motivational system that normally enables the subject to carry out the instructed task is being interfered with, more energy in the form of higher motivation level is required in the distraction than in the control condition to equal the same level of performance.

Dubrovsky delineated three methodological problems pertinent to ERP studies of psychopathology. First, EOG "cancellation" techniques (previously advocated by McCallum and Walter 1968 - *vide infra*), used to remove ocular contamination of the abnormal prolongation beyond CNV and known as post-imperative negative variation (PINV), could result in subtracting out the actual potential coming from the brain as well as that coming from the eye. A second problem concerned the making of electroclinical correlations based on single-session recordings. He suggested that several recording sessions were needed to establish adequate rapport between subject and experimenter to approach optimal performance. Third, the type of instruction given to the individual, whether patient or normal volunteer, has received insufficient attention in the study of CNV types.

Dubrovsky also reported substantive data on PINV and phobias to specific animals or objects (see Barbas and Dubrovsky, this volume). These findings show how instructional sets can be used as an independent variable in the manipulation of the amplitude and temporal character of CNV in psychopathological research. (Ed: Another relevant experiment reported by McAdam et al. in 1969 demonstrated that shape is affected in various ways by both external and internal instructional variables.) After patients had been treated by desensitization to previously phobogenic stimuli, the CNV takes on a "normal" shape.

Dubrovsky thought that too much concern was being given to relationships between early and late potentials and noted that the study of different types of brain potentials implicitly assumes that the nervous system works in an integrated, serial manner. Potentials measured in the frontal cortex reflect information that has already been processed in primary receiving areas. He suggested that the nervous system be considered as parallel, interacting subsystems that process information. For instance, visual input is processed initially in visual cortex and later in frontal cortex, but there is a modification of the information by other parallel subsystems as well. In studying CNV and psychopathology, Dubrovsky recommended the measurement and classification of amplitude and shape of slow ERPs in different clinical populations.

Knott commented that studies of late (or even later) brain potentials cannot ignore earlier potentials (including the far-field potentials) because early potentials carry information that can affect later activity. Conversely, the tonic level of the cortex created by processes related to slow late potentials associated with one stimulus can, in turn, affect early potentials evoked by the next stimulus. This has been shown by McAdam (1968, 1969). Tonic levels created by or associated with late potentials may be what "instructional set" is all about.

Knott also commented on the surprising lack of research on the association of P300 to psychopathology. If this potential can be modified experimentally, then whatever psychopathological states that have been mimicked in normals should make it useful in clinical populations both as a dependent and independent variable. Despite the substantial number of studies on P300 and psychological processes, very little has been done to establish the possible usefulness of P300 as an indicator of psychopathology.

Callaway questioned whether it would be simpler to assess schizophrenics by their verbalizations rather than distration-arousal measures. He focused on short-latency (less than 200-msec) ERPs and psychopathology (left half of Fig. 1) and pointed out two advantages to the use of these potentials. One was their apparent value in developing empirical diagnostic procedures, as exemplified by the work of E. Roy John (this volume). He also noted that earlier components may yield other methods of developing and testing theories about psychopathology and other aspects of individual differences. For example, schizophrenia is not a single disease entity. Some schizophrenics may have structural defects in short-term memory (involving information which can decay with a half-life of 250 to 200 msec and which does not enter consciousness). This type of memory is analogous to a buffered system used to construct filters. Callaway cited early studies (Callaway 1975) of segmental sets in schizophrenics that indicated variability in evoked responses within 90 to 200 msec. These results contrast sharply with work by Shagass (1976), which showed hyperstable evoked responses within the first 90 msec. Shagass has suggested that schizophrenics do not preprocess data properly so that when the stimulus comes in, other cerebral processes operate and no compensation occurs. This could account for the initial stable response and for the later variability. Callaway suggested that the later responses are being "gummed up" by other things happening in the brain in addition to processing of the stimuli. He saw the early evoked responses as not having been "tweaked up," and thus leading to highly variable late responses. Normal subjects, on the other hand, make immediate adjustments to incoming stimuli to compensate for whatever the brain may be doing at that moment and, therefore, compared to schizophrenics show more variability in earlier responses and more regularized or "tweaked" later responses.

Callaway noted reports that if a subject pressed a switch to perceive a stimulus, the evoked response to the stimulus (click) was depressed and the recovery cycle for full amplitude was about a second. This lag time suggests neural inhibition associated, perhaps, with ultra short-term (iconic) memory functions. He wondered whether schizophrenics would show perseveration of this type of neural inhibition. "Sick schizophrenics" (off medication) showed decreased amplitude of evoked responses in the 200- to 500-msec post-stimulus period. On the other hand, patients who were not as acutely ill did not show this decrease in amplitude (Braff et al. 1977). Although these techniques are not useful for diagnosing schizophrenia, they provide a good example of how early evoked potentials can contribute to our understanding of CNS functioning, particularly short-term memory.

Timsit-Berthier represented the right side of Fig. 1 in discussing CNV, its prolongation (PINV), and P300. (For fuller discussion see Timsit-Berthier et al., this section.) Briefly, four types of CNV shape, based on duration and resolution (return to baseline), were described: (1) rise of CNV between S1 and S2, resolving with slight positivity after S2; (2) rise of CNV between S1 and S2 and declining to baseline before S2; (3) rise of CNV between S1 and S2, continuing without diminution for seconds after S2; and (4) rise of CNV between S1 and S2, declining more slowly than Type II, but more rapidly than Type III. Also described was a "non-CNV," termed "flat." She suggested that CNV prolongation might represent an inversion of P300, and perhaps an extension out to "P600."

Positivity and negativity were expressed as a ratio, and those smaller than minus 0.1 with the inversion of P300 tended to be characteristic of psychotic individuals. Timsit-Berthier also asserted that these CNV types permitted discrimination of psychotic subjects from a control group. This classification permitted identification of 93 percent of neurotics (as opposed to psychotics).

Timsit-Berthier viewed the clinical application of ERPs as involving the differentiation, by cumulative curve measurements including shape, of psychotic and neurotic populations rather than the differentiation of psychotic and normal individuals. (No evidence of discrimination of neurotic from control subjects was apparent, which makes an either-or discrimination of "psychotic" from "neurotic" rather problematical!)

Abraham advocated the use of the "Present State Examination" (Wing et al. 1967), a method of psychiatric assessment reputed to have cross-cultural validity. This twofold assessment provides both a qualitative description and a quantitative measure of the condition. It permits bypassing diagnostic labels and provides assessment of different areas of total personality disturbance, thus yielding a measurement of functional impairment and psychopathology, independent of psychiatric diagnosis. The Present State Examination was reported to have inter-observer reliability and to be quantitatively related to physiological variables. Indeed, Abraham wondered why Timsit-Berthier stopped her measurements at physiology and did not also measure psychiatric state. He thought it more important to study types of psychopathological disturbances that can be measured consistently in different laboratories rather than nebulous diagnostic categories. In his own work, he reported that the joint use of the Spiral After Effect (SAE) test and the Present State Examination has improved discrimination among diagnostic categories of psychiatric patients.

In a post-Congress memorandum of consensus prepared after discussions with Dongier and Timsit-Berthier, Abraham stated: "CNVs can and do assist in psychiatric assessment, and an understanding of the processes underlying psychiatric disorders, provided that there is standardization of procedures (within and between laboratories), adequate quantification of data, and selection of suitable differential diagnoses." Abraham claimed, "... when the CNV values are extremely abnormal, the probability that the subject is suffering a psychotic opposed to a neurotic illness may be as high as 20:1." He further stated "... given a substantial sample of data from the individual subjects: (1) the pre-imperative amplitude of the CNV, (2) the post-imperative negativity divided by that amplitude value, (and) (3) the duration of the Spiral After Effect ... objectively, consistently, and with substantial confidence when taken together, discriminate between severely disturbed and healthy individuals."

Abraham further pointed out that Small and Small (1971), Abraham et al. (1976), and Timsit-Berthier, Delaunoy et al. (this section) agree that severely ill psychotic patients have (1) lower amplitude pre-imperative negativity and (2) higher amplitude post-imperative negativity than do "healthy subjects"; and that (3) these findings are persistent over an extended period of observation. Thus, in his opinion, there was greater agreement on the use of CNV in psychiatry than generally supposed. He also pointed out that electrophysiological data from the realm of slow potentials yield objective information not dependent upon subjective observations based upon patients' verbalizations or psychiatrists' qualitative opinions.

Lelord described a sensory (sound-light) conditioning paradigm that requires no overt responses (detailed elsewhere in this section). Subject groups include schizophrenic and neurotic adults, schizophrenic children, and normal controls. Auditory potentials (to S1) were less obvious in schizophrenics than in neurotics and normals. Visual evoked potentials (to S2 at occiput) were also less obvious in schizophrenics than in normals; however, there were no group differences in interstimulus slow potentials (CNVs).

Autistic children showed CNVs and conditioned evoked potentials that were smaller than those in normal children. Mentally retarded children had fewer evoked potentials at the occiput and more generalized positive slow potentials.

Thus, the late potentials in this paradigm do not discriminate psychotics, but they may discriminate autistic from normal children. Earlier potentials appeared to be discriminative. The similarity of neurotics and normals in the Timsit-Berthier paradigm for CNVs thus holds in this experiment. Different effects in children and adults may require further experimental consideration.

There is a paucity of information in man on the electrogenesis of ERPs, possibly because of difficulty in obtaining suitable clinical material. *Zappoli* cited data from six clinical cases involving Freeman-Watts frontal plane sections for lobotomy operations (see Zappoli et al., this section) as being incompatible with the findings of Skinner (this volume) that medio-thalamic fronto-cortical systems were important for the genesis and regulation of anterior frontal negative slow potentials. The CNV development of lobotomized patients indicated that prefrontal brain regions, when isolated from normal connecting pathways with thalamic nuclei, continue to receive and process information of relevant stimuli, possibly under the control of cortical and nonspecific subcortical pathways outside the thalamic projection system. (Ed: Despite the problems of phylogenetic differences, some progress has been made in the study of ERP electrogenesis and neurochemistry in subhuman species).

Marczynski (this volume) has reviewed a wide range of electrophysiological, pharmacological, behavioral, and psychopathological data and has proposed a model that may be useful to clinical investigators relating drugs and changes in slow potential patterns.

* * *

The Symposium was thrown open to general discussion.

Weinberg inquired why measurements of reaction time were necessary to make inferences about processing irrelevant stimuli in Tecce's distraction paradigm. Tecce replied that without performance decrement in a central task, the efficient processing information in two tasks is a matter of divided attention, whereas distraction implies some type of performance decrement in a central task. He then offered a formal definition of distraction as a hypothetical organismic process that directs attention toward irrelevant stimuli in the environment (internal or external) and interferes with the selection of relevant stimuli resulting in response decrement to the relevant stimuli. Thus, Tecce emphasized the importance of impaired performance in a central task as a critical attribute of the distraction process and as one of two criteria suggested earlier for a "CNV distraction effect," the other requirement being evidence that the stimuli extraneous to the central task have been processed (Tecce and Hamilton 1973). He suggested that Knott would probably regard "distraction" as causing "stress" but that the concept of "distraction-arousal" might be more experimentally testable and that Callaway's notions of "gummed up" or "tweaked up" had too much surplus meaning to be useful as theoretical constructs.

Knott responded that stress was a more inclusive term and that the environmental manipulation that causes "distraction" introduces competing stimuli and causes stress as an organismic response. He felt that Tecce's own data suggest the validity of this argument, since the stress occurring in consequence of distracting environmental stimuli is associated with elevated heart rate and increased eyblink rate, which Tecce calls "arousal" (Tecce 1971). "Stress" may be induced by a variety of internal and external manipulations; "distraction" is one of these.

The issue whether distraction and arousal are subconstructs of stress is similar to a previous controversy whether attention and arousal are subconstructs of motivation (Tecce 1972). Since distraction connotes a disruption in the steering functions of attention (stimulus selection) and since arousal is devoid of such associative properties, stress, in encompassing both distraction and arousal, would appear to include both steering and energizing properties, and consequently, have broader explanatory value. Distraction and arousal, on the other hand, being narrower in scope appear to have less imprecise meaning and lend themselves more readily to experimental testing. The question of whether stress connotes only impairment in performance, as postulated for distraction, or also connotes beneficial effects on behavior, requires clarification both conceptually and experimentally. Tecce viewed concomitant elevation in heart rate and eyeblink rate as reflecting a negative (stressful?) hedonic state.

Abraham's strategy of direct observation of patients rather than reliance upon their verbalizations was regarded by Tecce as important. He pointed out, however, that electrophysiological measures are generally more reliable than psychiatric observations. In response to Callaway's suggestion that simple verbalizations of patients might be as useful as electrophysiological measures, Tecce reiterated the marked disagreement among psychiatrists in interpreting verbalizations of patients and pointed out that Callaway's proposal could not be followed with mute patients. Included under the mantle of "electrophysiological measures" would be the topographic distributions of CNVs in normal states and their disruption under conditions of altered environmental manipulation or in association with psychopathological states.

Knott raised the point that the shape and topography of the CNV process required further definition, experimentation, and discussion. Tecce has proposed two "types" of CNV based upon morphology of the ascending negativity (Tecce 1971) and added a third type with a triphasic time course (Tecce and Cole 1976). Timsit-Berthier (this section) has proposed four types of CNV. Earlier, van Veen et al. (1973) showed that there were three morphological types based upon the development of pre-S2 negativity. These were related to personality factors defined by Witkin's "perceptual mode" of field dependency (Witkin et al. 1962).

The suggestions introduced by Timsit-Berthier (this section) regarding the inversion of P300 as a causal factor in prolonging the CNV (the PINV) clearly need experimenting testing. This provides an opportunity for investigators (whose field defects leave only the right lower quadrant intact) to discover whether such inversion is possible in normal subjects and to define the instructional/environmental conditions eliciting the proposed effect (cf. Delaunoy et al., this section). Conceivably this could serve as a "model" for a psychopathologic process.

Dongier discussed the problem of defining patient groups by challenging Abraham's position on the "Present State Examination." He felt that other methods might prove more profitable in the exploration of diagnostic and descriptive correlates of electrophysiological processes. Dongier also questioned the change of CNV in schizophrenics subsequent to administration of drugs. Tecce responded that abnormally low-amplitude CNVs are increased by mesoridazine and thioridazine in chronic schizophrenics and that psychopathology, particularly hallucinations, shows a concomitant decrease. These pharmacologically produced alterations in CNV were different for frontal, central, and parietal areas. He called this phenomenon "topographical discordance."

Knott added that variability in the topography of slow potentials has been well documented with evidence that indicates "the CNV" represents a multiplicity of brain potentials having different spatial and temporal characteristics. A complete account of "processing" in CNS awaits analysis of these variables and correlation with well-defined operational variables ("normal" and psychopathologic) on the behavioral side.

Returning to problems of methodology, Rosen asked to what extent eye movement potentials contributed to what is regarded as cortically generated CNV. Tecce replied that the combined use of visual fixation, careful off-line exclusion of trials with clearly present eye movements, and evaluation of averaged vertical EOGs for averaged CNV trials provided collective protection against ocular contamination of CNV measurement. Peters et al. (1970), for instance, have described very precise measures for the identification of eye movements. This method takes account of the fact that potentials of cerebral origin spread into derivations below the eye and may be recordable from points quite remote from scalp derivations. The method for "cancellation" of eye movements mentioned by Dubrovsky (*vide supra*) may also "cancel" the CNV. Whether one uses manual or programmed computer methods for acceptance or rejection of individual trials, it is indeed necessary to keep the baby clean as well as to guard against throwing out the baby with the bath water, as has been reported for the potentiometer method (Waszak and Obrist 1969).

In summary, the panel agreed that psychiatric subject populations required more rigorous definition, although the precise means of such determinations could not be established. There appeared to be considerable innovation in the manipulation of CNV as a dependent variable with experimental analogs of psychopathology. Evaluation of experimental and clinical data will continue to require close attention to the exact experimental methodology employed. Indeed, basic conclusions regarding process may be entirely dependent upon these independent variables. Divergence of methods in measurement of slow potential data persists, no unanimity of choice has emerged, and it is an open question whether early or late ERPs carry the most relevant information with respect to normality versus pathology. Although explanatory hypotheses are alive and competing, some future rapproachment seems probable, as evidenced by comparisons of the "stress-ceiling" hypothesis and the "distraction-arousal" hypothesis. Such hypotheses make it possible to construct testable models of electrocortical pathology. Finally, the usefulness of temporo-spatial descriptors of the total process of event-related potentials (note the plural) may make it possible to obtain a more precise electrical brain picture (the literal translation of "electroencephalograph") in relation to behavior.

This section was initiated with a provocative question: Why is slow potential research in psychiatry unproductive? The contents of this section indicate that the research has been more productive than initially believed, particularly in terms of possible hypothetical constructs. (There were only eight papers directly addressed to psychopathology presented at the previous two Congresses, and only six at this one!) The utility of slow potential techniques in individual psychiatric assessment, however, requires further validation and awaits further definitive investigations.

EXPERIMENTAL PRODUCTION OF POST-IMPERATIVE NEGATIVE VARIATION IN NORMAL SUBJECTS [1]

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Several years ago, the Liege laboratory (Timsit-Berthier et al. 1972, 1973) reported that contingent negative variation (CNV) is abnormally prolonged for several seconds in most psychotics and some neurotics. This phenomenon is called postimperative negative variation (PINV). Transitory PINVs have occasionally been observed in normal subjects under stressful conditions. Gauthier and Gottesman (1976), for instance, produced PINVs by superimposing labyrinthine stimulation and a mental reckoning task on a classical CNV paradigm.

What psychophysiological parameters control the appearance of PINVs in normal subjects? The present study was designed to elicit PINVs experimentally in normal subjects by subtle modification of a classical CNV paradigm.

Methods

The subjects were 15 women from 25 to 55 years old (mean age: 31.5 ± 6.2) who were applicants for a marriage counselor position. The experiment was conducted during job interviews, which ensured high motiviation of the subjects and, presumably, CNVs of high amplitude. To eliminate neurotic or psychotic subjects, clinical interviews were conducted and projective tests were administered.

Vertex EEG referred to the left mastoid was recorded using Ag/AgCl electrodes and an 11-sec time constant. The electrooculogram (EOG) was recorded from right infra- and supra-orbital electrodes and the galvanic skin response (GSR) from electrodes applied to the thenar eminence (active) and dorsal surface (inactive) of the left hand. Atropine (0.25 mg for two electrodes) was injected subcutaneously at vertex and mastoid electrode sites in three subjects to control for GSR artifact. Electrophysiological data were averaged in 8-sec epochs at 128 Hz with an Enhancetron Computer.

Two paradigms were used to elicit the CNV and PINV:

1. *Situation A.* In a standard CNV paradigm, a click (S1) was followed after 1.5 sec by a train of light flashes (S2) (0.28 joule, 18 Hz) terminated by pressing a button.
2. *Situation B.* Stimuli were presented as in Situation A except that the flashes continued for 1 sec, regardless of response, in one-third of the trials selected at random.

A modified ABA sequence was used as follows: A (36 trials), B (24 trials), and A (12 trials). Six CNVs were thereby obtained for each subject by averaging successive blocks of 12 trials. Trials contaminated by GSR or EOG artifact were rejected from averages.

PINV duration was measured from S2 onset to the point at which the signal returned to baseline. It should be noted that averages obtained during conditions A and B were not strictly comparable since the duration of flashes was longer in the four B trials not terminated by button pressing.

Results

Distinct prolongation of the CNV beyond S2 was observed in ten subjects. In these subjects, PINV duration increased from less than 2 sec (situation A) to 4.5 to 6 sec (situation B) and then decreased again when situation A was reinstated. Fig. 1 illustrates the experimental production of a transitory and reversible PINV in one subject.

Situation B did not produce PINVs in the remaining five subjects. Four subjects in the group, however,

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[1] This work was supported in part by Grant 20397-FRSM.

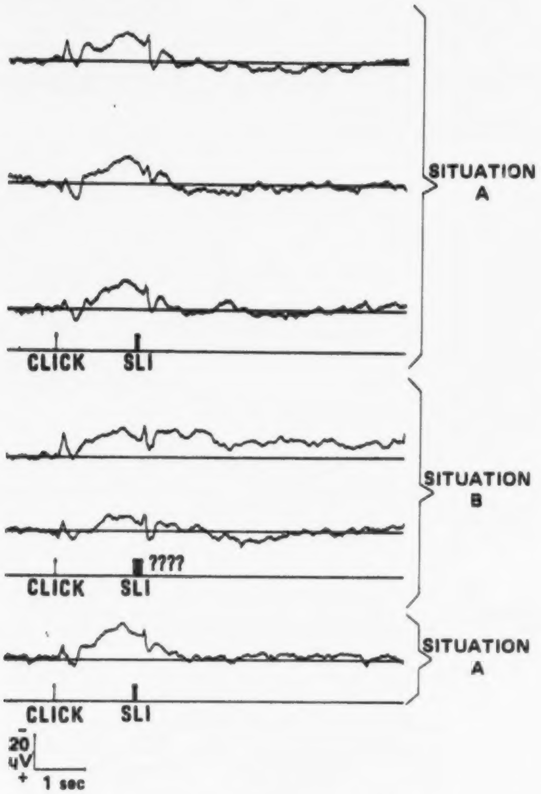

Fig. 1. Representative waveforms observed in a normal subject during a classical CNV paradigm (situation A) and a modified paradigm in which the key press did not terminate the imperative stimulus train on one-third of the trials (situation B). Postimperative negative variation appeared during situation B and then disappeared when the normal stimulus-response contingencies were reinstated (situation A, bottom trace).

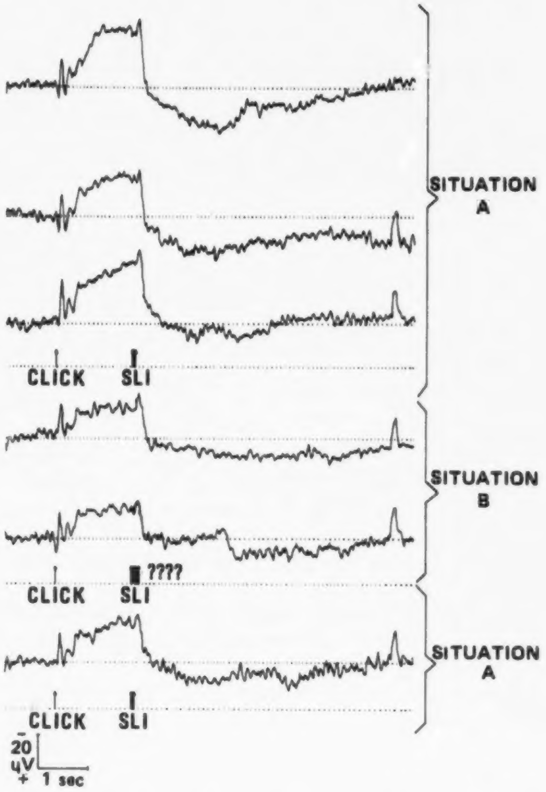

Fig. 2. Waveforms observed in one of four subjects who did not exhibit PINV during situation B. Note the large positive slow potential shift following S2 (SL1) in this subject during situation A. This positive shift was considerably reduced in the four subjects during situation B.

exhibited high amplitude postimperative *positive* waves in situation A, a feature that was not present in the PINV group. Fig. 2 illustrates this distinctive feature. In these subjects, there was a reduction of postimperative positivity in situation B.

Upon completion of the experiment, subjects were asked what they thought had happened during situation B. Subjects in whom PINV was observed did not understand what had happened or could not provide an explanation. Non-PINV subjects rationalized that the experimenter had interfered with the apparatus or that an equipment malfunction had occurred.

Discussion

Two-thirds of the subjects in this experiment showed substantial prolongation of PINV following a small modification of the experimental protocol. It is possible that the prolonged negative wave as an electrodermal artifact elicited by the change in stimulus-response contingencies of situation B. Raskin et al. (1969) and others have shown that the GSR is an important component of the orienting reaction to novelty. Averaged palmar skin responses, however, showed no resemblance to waveforms recorded simultaneously at the vertex. As a further precaution, scalp recording sites were atropinized in three subjects. PINVs were observed in all of these subjects. It is unlikely, therefore, that the experimentally produced PINVs were an electrodermal artifact.

Two subgroups of subjects were distinguished on the basis of the appearance or absence of PINV in situation B and by the presence of absence of postimperative positivity in situation A. The latter positivity was not present in any PINV subjects, although the significance of this observation is not presently understood. Results of the *a posteriori* interrogation of subjects provide a possible clue. Prolongation of the PINV was observed in subjects who were *unable to resolve* *the ambiguity* of the experimental intervention, whereas, PINVs did not appear in subjects who were able to resolve the uncertainty of the situation, regardless of the correctness of the explanation.

Donchin (1968) proposed that a large positive wave, peaking about 250 msec after stimulus onset, reflects the resolution of uncertainty. A vast literature (summarized by Tueting, this volume) associates this positive component (P300) with a variety of cognitive events and decision-making processes. The large postimperative positive wave observed in non-PINV subjects is probably related to the P300 component. Absence of this waveform in subjects who failed to resolve the uncertainty of the experimental intervention is consonant with Donchin's (1968) proposal.

PINVs have been observed in at least four situations: (1) in normal children less than 10 years old (Timsit-Berthier and Hausman 1972), Low and Stoilen 1973); (2) in normal adults under stress (Gauthier and Gottesman 1976); (3) in psychotic patients with poor prognoses (Timsit-Berthier et al. 1972, 1973); and (4) in patients with organic brain damage (Paty et al., in press). PINVs tend to be transitory and reversible in normal adults under stress, but irreversible in psychotics.

Results of the present study confirm the findings of Gauthier and Gottesman (1976) that PINV can be experimentally produced in normal adults. The diversity of conditions and populations in which the PINV has been observed, however, suggest that it probably is not a unitary phenomenon. Further study is needed to establish the functional significance of component processes contributing to postimperative negative variation.

Summary

Fifteen normal subjects participated in two experimental paradigms: (1) a classical CNV paradigm and (2) a modified CNV paradigm in which motor response did not terminate S2 in one-third of the trials. In the second situation, a prolongation of postimperative negativity was observed in two-thirds of the subjects. *A posteriori* questioning suggested that subjects showing prolonged PINV were unable to resolve the ambiguity of the experimental intervention, while subjects showing no prolongation were able to rationalize what had happened.

EFFECTS OF VISUAL DISTRACTION ON CONTINGENT NEGATIVE VARIATION AND TYPE A AND B CNV SHAPES[1]

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The auditory presentation of letters within the interstimulus interval of a classic CNV paradigm (Walter et al. 1964) produces a reduction in CNV amplitude and lengthened reaction time (RT) to S2 (Tecce et al. 1976). This CNV distraction effect is accompanied by elevated levels of psychophysiological arousal (increased heart rate and eyeblink rate). The purpose of the present study was to test the generality of this distraction-arousal association in a short-term memory task for visual letters and to assess the CNV distraction effect in two groups of individuals characterized by basal CNVs with fast (Type A) and slow (Type B) rise times. The A-B typology has been shown to be related to individual differences in response to amphetamine (Tecce and Cole 1974) and phenobarbital (Tecce et al. 1977).

Method

Subjects

Twenty-four male college undergraduates served as paid volunteers. Age range was 18 to 25 ($\bar{X}=20.3$). Twenty individuals were right-handed and four were left-handed. All participants were screened for possible medical and psychiatric problems.

Experimental procedures

A simple reaction time paradigm with a constant foreperiod constituted the basic experimental procedure. A preparatory signal (S1) consisted of a brief (0.15-sec) flash of a black "X" (2 cm in height) appearing on a circular patch of dim light (2.5 cm in diameter), which was projected onto a translucent plastic panel 5 cm in height and 4 cm in width. The projector was located 1 m from the subject's eyes at an approximate angle of 25° from the horizontal and stood 44 cm from the floor. The second stimulus (S2) was a 1000-Hz tone of approximately 70 dB (SPL) presented through earphones 1.5 sec after the "X" and terminated by a telegraph key press. All but one subject pressed the key with the right hand. A control run (C) consisted of 16 trials of S1-S2-motor response and lasted approximately 4 min. Intertrial intervals varied randomly from 8 to 14 sec ($\bar{X}=11$) within a rectangular distribution of values 1 sec apart. In addition to the control run, there were two letter conditions - visual letters-recall (R) and visual letters-no recall (NR). The letters-no recall task was similar to the control condition except that four letters were presented through the visual projector within the S1-S2 interval. The letters A, C, E, H, K, L, N, P, S, and U could appear with equal probability. Letter exposure time was 0.2 sec and interletter interval was 0.1 sec. The time interval between the fourth letter and tone (S2) onset was 0.15 sec. Subjects were instructed to ignore the letters in this letters-no recall condition and to concentrate only on terminating the tone. The letters-recall task was similar to the no-recall task except that upon hearing "OK" spoken by the experimenter, subjects repeated the four letters in the same order as presented. The "OK" signal for information feedback occurred irregularly from 1 to 4 sec after the key press.

Subjects were randomly assigned to two groups. The first group (n=13) received the test sequence: C1-C2-C3-R-C4-NR-C5; the second group (n=11) received C1-C2-C3-NR-C4-R-C5. (Two subjects were dropped from the second group due to technical problems.) The first two control conditions were not considered in data analysis. Prior to the sequence of test runs, subjects received a 15-min rest period. A test run was given every 10 min (4-min test and 6-min rest). Session duration was approximately 1½ hours. The testing room (3.8 by 4.5 m) was dimly lighted by a floor lamp with a 60-W incandescent bulb. Subjects were seated in a semireclined position and were encouraged to keep their eyes on the stimulus panel and to avoid blinking during presentation of stimuli. Behavior was monitored on closed-circuit television. Verbal communication took place through a two-way intercom system.

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[2] Research Scientist Development Awardee 1-K02-00016 from the National Institute of Mental Health.

Recording procedures

EEG was recorded from Fz, Cz, and Pz with linked earlobes as a reference. EOG was recorded from 3.0 cm above and 2.0 cm below the right eye as measured from center to center of pupil and electrode. Electrodes were Beckman Ag/AgCl standard (EEG) and miniature (reference and EOG) types. A Grass Model 7B polygraph was used to record EEG and EOG. The time constant for EEG and EOG was 8 sec. High-frequency cutoff was 75 Hz (50% amplitude reduction) with 12 dB per octave roll-off. CNV and EOG data were recorded on magnetic tape. Trials with eye movements (16% of total trials), premature key presses within the S1-S2 interval ($<1\%$ of total trials), and extraneous baseline shifts, such as those produced by body movements (27% of total trials), were omitted in off-line averaging with a CAT 1000. Average CNVs were based on 6 to 12 trials per run, the number being constant for a given individual. CNV amplitude was measured as the difference in average voltage (sampled every 16 msec) between the 256-msec epoch pre-S2 and the 512-msec epoch pre-S1; this difference was referenced to an on-line 25-μV calibration pulse. The EKG for cardiotachometric analysis was recorded from sternum to lower left chest. Overall heart rate (beats per minute) for each condition was determined by obtaining the mean of a random sample of 20% of individual momentary heart rate in a 4-min run (20% and 100% samples yield comparable results). Eyeblinks were defined as an EOG excursion of at least 50 μV and of less than 1000-msec duration (usual duration: 150 to 300 msec) as measured at the EOG baseline. Eyeblink rate (blinks per minute) was based on the number of blinks occurring during an entire 4-min run. In the letters-recall condition, accuracy of recall (percent correct trials) was determined by dividing the number of trials in which recall of the four letters was correct by 15 (total number of trials scored). A trial was correct if letters were repeated in the same sequence given.

Type A and B CNV shapes

Subjects were classified into two groups on the basis of CNV shapes. Fig. 1 shows two types of CNV determined by a fast rise time (Type A) and a slow rise time (Type B) (Tecce 1972). The slope of the negative-going (ascending) limb of CNV was determined by comparing a 112-msec EEG epoch occurring 760 to 872 msec after S1 (point L in Fig. 1 is the midpoint of this segment) with an epoch occurring 256 msec before S2 (point H in Fig. 1 is the midpoint of this segment). The value of L represents the mean of eight voltages sampled 16 msec apart. A small voltage difference (less than 6 μV) between L and H (HD on left side of Fig. 1) indicates a quick rise time and a Type A shape. A large voltage difference (6 μV or more) between L and H (HD on right side of Fig. 1) indicates a gradual rise time and a Type B shape. As in previous work (Tecce and Cole 1974, Tecce et al. 1977), this quantitative determination of the A-B typology is based on Cz recordings made during the control conditions (C3 run in this study).

Statistical analyses

For comparisons between letter and no-letter conditions, mean differences were evaluated by correlated *t*-tests with 23 degrees of freedom. For comparisons between Type A and Type B groups, mean differences were evaluated by independent *t*-tests with 22 df. Unless otherwise specified, reported differences are significant at $p < .05$.

Results

Preliminary evaluation of CNV amplitude, RT, heart rate, and eyeblink frequency for control runs occurring before and after letter conditions showed that the three controls were not different from one another on each response measure. Consequently, data for these three control conditions were pooled for statistical evaluation. Tables 1 and 2 contain summaries of means, standard deviations, and significant comparisons among experimental conditions for the response measures. For simplicity of presentation, CNV negativity appears as algebraically positive in the tables.

Measurements

Table 1 contains mean values of CNV amplitude for pooled controls and for letter conditions for Fz, Cz, and Pz locations. For Fz and Cz, mean CNV amplitude was lower for the letters-recall than the letters-no recall condition ($p < .05$). For each recording site, mean amplitude of CNV was lower in both the letters-recall and letters-no recall condition compared to the pooled controls ($p < .001$). Fig. 2 shows representative CNV data for one subject.

An evaluation of topographical differences for pooled controls indicated that CNV amplitude was larger at Cz than at Pz ($p < .001$) and larger at Pz than at Fz ($p \leq .001$). The mean difference between Cz and Fz ($\bar{X}_{Diff} = 8.35\ \mu V$; $SD_{Diff} = 6.18$) was significantly ($p < .001$) larger than the mean difference between Cz and Pz ($\bar{X}_{Diff} = 4.33\ \mu V$; $SD_{Diff} = 4.37$).

As shown in Table 1, mean RT was slower for the letters-recall condition than for either the letters-no recall condition or pooled controls ($p < .001$). Mean heart rate and eyeblink rate were higher in the letters-recall condition than in either the letters-no recall condition or pooled controls ($p < .001$). For the letters-recall condition, mean percent of trials with correct recall of letters was 75.58 (SD = 24.01).

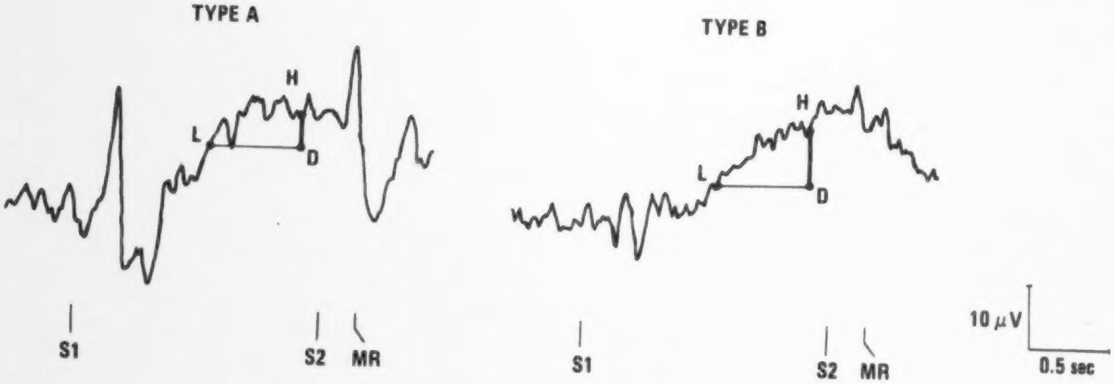

Fig. 1. Two types of CNV shapes based on fast (TypeA) and slow (Type B) rise times. Type A has a difference of less than 6 μV between l and H (shown as HD). The L-H difference is 6 μV or greater for Type B. The recording site is Cz with linked earlobes as reference. Relative negativity at Cz is upward.

Table 1. Electrophysiological Measures and Reaction Times – Means (Standard Deviations)

Condition	CNV amplitude, μV			Reaction time, msec	Heart rate	Eyeblink rate
	Fz	Cz	Pz			
Letters-recall	-1.12[a, b] (6.43)	5.55[a,b] (6.30)	2.16[b] (5.24)	392[a, b] (135)	76.20[a, b] (10.26)	20.15[a, b] (11.33)
Letters-no recall	2.30[a, b] (4.98)	8.69[a, b] (7.33)	4.29[b] (4.74)	239[a] (47)	71.61[a] (9.61)	12.40[a] (8.78)
Pooled controls	4.82[c] (3.20)	13.17[c] (7.12)	8.84[c] (5.63)	234 (42)	71.07 (9.93)	12.57 (8.32)

[a] Letters-recall and letters-no recall significantly different from each other.

[b] Significantly different from pooled controls.

[c] Significant differences: Cz > Pz > Fz.

Table 2. Electrophysiological Measures and Reaction Times for Type A and B Groups during Pooled Control Conditions—Means (Standard Deviations)

Response groups		CNV amplitude, μV			Reaction time, msec	Heart rate	Eyeblink rate
Group	n	Fz	Cz	Pz			
Type A	12	4.37 (3.29)	10.85 (7.60)	6.25[a] (5.35)	250.33[b] (52.64)	74.02 (9.35)	11.66 (9.11)
Type B	12	5.27 (3.17)	15.49 (6.04)	11.43[a] (4.80)	217.92[b] (20.65)	68.12 (9.99)	13.48 (7.74)

[a] $p < .03$ [b] $p < .08$.

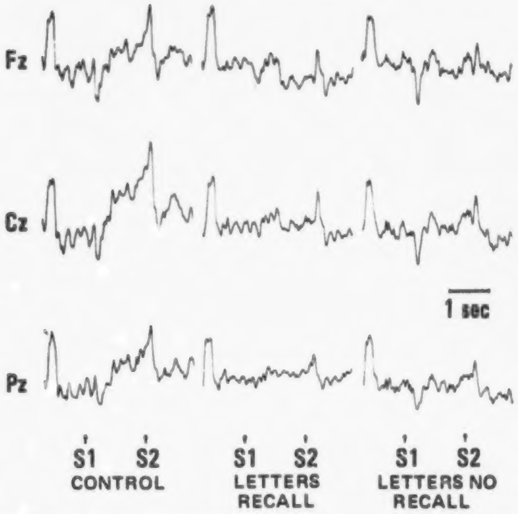

Fig. 2. Examples of CNV traces of one individual for control, letters-recall, and letters-no recall conditions for frontal (Fz), central (Cz), and parietal (Pz) recording sites. The S1-S2 (flash-tone) interval was 1. 5 sec. The on-line calibration signal at the left of each trace is 25 μV. Relative negativity at Fz, Cz, and Pz (referred to linked earlobes) is upward.

Type A and B CNV shapes

The criteria described above for classification of CNVs by difference in CNV slope resulted in 12 Type A and 12 Type B individuals. For the C3 run, which was the basis for determining these types, three A's and two B's had absolute Cz CNV amplitudes less than 6 μV while nine A's and ten B's had amplitudes greater than 6 μV. Table 2 indicates that the Type B group shows a pattern of higher CNV amplitudes (for pooled control conditions) than does the Type A group ($p < .03$ for the Pz recording site). These points are discussed further below.

Fig. 3 presents the differences in CNV amplitude for control minus letters-recall. The larger this difference, the relatively smaller is the value of CNV amplitude in the letters-recall condition. For all three recording sites, Fig. 3 indicates that there is a relatively greater decrease in CNV amplitude for the Type B group in the letters-recall condition than for the Type A group. For Fz, this difference approaches statistical significance ($p < .07$).

Table 2 indicates that Type B subjects tended to have a faster mean RT (218 msec) than did the Type A group (250 msec) ($p < .08$). Means of heart rate and eyeblink rate for the two groups also appear in Table 2. Mean percent of trials with correct recall of letters was 76.26 (SD = 24.02) for the B group and 74.89 (SD = 23.99) for the A group.

Discussion

There were two main findings in this study. First, CNV amplitudes were reduced during a short-term memory task as compared to a simple RT paradigm. The criteria for demonstration of a distraction effect appear to have been fulfilled: (1) stimuli in the irrelevant (distraction) task were processed (75% recall of letters was achieved) and (2) a performance decrement in the central (nondistraction) task resulted (significant slowing of RT when recall was required). This finding replicates the distraction effect on CNV observed with a similar short-term memory task for auditory letters (Tecce et al. 1976). Other studies have shown CNV reduction in a visual short-term memory matching-to-sample task (Roth et al. 1975) and in a task involving extraneous auditory (music) stimulation (Miller et al. 1973).

The second main finding was that visual stimuli produced a distraction-arousal association that replicates previous results with auditory distraction: reduced CNV, increased RT, elevated heart rate, and increased eyeblink frequency. Consequently, these data extend the generality of the distraction-arousal hypothesis and suggest that this hypothesis provides a useful model to account for disruption in CNV development.

In addition, the four measures (CNV, RT, heart rate, and eyeblink rate) are considered to covary reliably for both auditory and visual distraction, comprising a reliable pattern of disturbed neuropsychological functioning that might be of value in the assessment of abnormal neurological and psychiatric conditions. In a recent study of psychosurgery, patients having a more favorable postoperative outcome showed a pattern of higher CNV amplitude (at Cz and Pz), faster RT, and lower heart and eyeblink rates compared to patients having a less favorable outcome (Tecce 1977). Eyeblink rate differentiated the two patient groups most clearly.

Although eyeblinks are a serious source of artifact in the recording and measurement of CNV, they appear to have value, *per se*, as a dependent variable and indicator of psychological disturbance. The joint occurrence of elevations in eyeblink rate and heart rate in the letters-recall condition was accompanied by subjective evidence (verbal reports) that the short-term memory task was a demanding and unpleasant experience. We infer, therefore, that elevations in heart rate and eyeblink rate, considered jointly, are potentially useful indicators of negative hedonic experience. Previous work has shown that a dissociation of these two measures (*increase* in heart rate and *decrease* in eyeblink rate) following dextroamphetamine administration is related to euphoria and feelings of well-being—i.e., a positive hedonic experience (Tecce and Cole

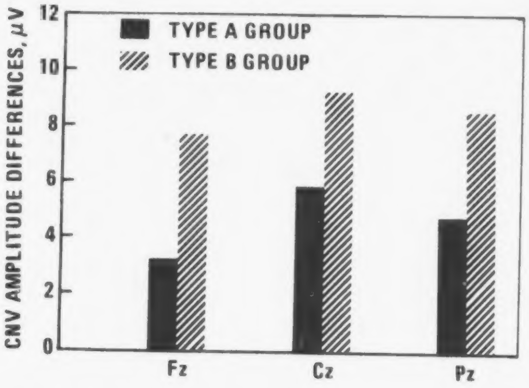

Fig. 3. CNV amplitude differences (control minus letters-recall) for subjects having basal CNVs with a fast rise time (Type A group–n=12) and a slow rise time (Type B group–n=12). Larger difference scores indicate greater CNV reduction in the letters-recall task compared to pooled control values. For the letters-recall condition, means (and standard deviations) of CNV amplitude values were; Fz, 1.03 (5.54); Cz, 5.00 (3.85); and Pz, 1.47 (2.75) for the Type A groups and Fz, -2.44 (6.19); Cz, 6.10 (8.21); and Pz, 2.85 (6.99) for the Type B group. For simplicity, negative CNV values appear as positive.

1976). These findings suggest that elevated heart rate accompanied by decreased eyeblink frequency may reflect an emotional state associated with positive hedonic tone (as in an amphetamine experience), but that increased heart rate accompanied by increased eye blink frequency probably indicates an emotional state associated with negative hedonic tone (as during distraction). Further discussion of the eyeblink-hedonic hypothesis appears elsewhere (Tecce et al. 1978).

The anterior-posterior distribution of amplitude of CNV recorded in control (no-letters) condition showed a steeper fronto-central than parieto-central gradient of CNV development. This ordering of CNV amplitude values (Cz > Pz > Fz) and the greater steepness in the fronto-central gradient of CNV development in comparison with the parieto-central gradient are in agreement with previous work (Tecce et al. 1976) and suggest two indices of normal CNV topography of potential value in the assessment of brain dysfunction in individuals having neurological and psychiatric problems.

The present results on the CNV distraction effect, distraction-arousal coupling, and topographical CNV distribution agree with previous work, while other aspects of the present findings do not. First, in the earlier study (Tecce et al. 1976), when auditory letters were presented in the S1-S2 interval with instructions that no recall would be required and that they could be ignored (letters-no recall), amplitude of CNV was not changed. In the present study, on the other hand, visual letters significantly reduced CNV amplitude even when no recall was required. This unexpected decrease in CNV amplitude appears to be related to the use of the four successive visual letters as a chain of anticipatory stimuli, the fourth letter appearing consistently 150 msec before S2 (tone) and, therefore, serving as a cue for tone onset. In postexperiment reports, subjects indicated attending to the extraneous letters (despite instructions to ignore them) in order to facilitate preparation to respond to S2. Such a use of the extraneous letters was inadvertently facilitated by asking the subjects to fixate on the projection screen in order to avoid unnecessary eye movements. The auditory-letters task did not lend itself as readily to such usage of extra-task cues, partly because the spoken letters were characterized by asynchronous properties that are intrinsic to human speech. In the present task, the automated presentation of the extraneous visual letters produced a predictability that was lacking for the auditory letters.

The foregoing analysis suggests that in the visual letters-no recall task self-instructed sets to process letters occurring within the S1-S2 interval may have made a distraction task out of what was intended to be a nondistracting one. If so, the question arises as to why the use of letters as facilitating cues did not result in faster reaction times in the letters-no recall condition (239 msec) compared to the control condition (234 msec). One possibility is that whatever facilitation in reaction time resulted from the usefulness of extraneous letters as cues was offset by the disruption of a unified attention set to S2. In addition, it may not be possible to improve upon reaction time in the control condition, where an individual may already be at an irreducible physiological limit. In any case, the fact that a decrease in CNV amplitude occurred in the letters-no recall condition without changes in heart rate and eyeblink rate suggests that part of the reduction in CNV magnitude occurring in both visual and auditory letters-recall tasks may be reflecting interference with a cognitive process independent of changes in psychophysiological arousal level. Furthermore, to the extent that reaction time reflects a process of motor readiness, the reduction of CNV amplitude in the letters-no recall condition *without* associated changes in reaction time suggests that part of the complex called "the CNV" is independent of motor preparation (Tecce 1972).

Despite the unexpected reduction of CNV amplitude in the letters-no recall condition (where distraction should have been minimal or nonexistent since letters could be ignored), there was significantly greater CNV reduction during the letters-recall task (where recall of letters was intended to heighten distraction). We interpret the greater disruption of CNV development in the short-term memory task (letters-recall) as due to greater distraction produced by the complex cognitive activity required in processing the substantive properties (meaning) of the extraneous letters, i.e., remembering the letters themselves, in contrast to the simple cognitive functioning involved in processing the formal properties of the letters (as cues or events to facilitate response to S2) as in the letters-no recall task. By similar logic, since psychophysiological arousal levels were selectively increased in the letters-recall task but not in the letters-no recall task, it appears that a necessary condition for the joint occurrence of distraction and arousal changes (distraction-arousal coupling) is the kind of higher level brain functioning involved in processing information of a substantive nature, such as the lexical content of letters in the present study.

The pattern of lowered CNV amplitudes and slower RT shown by Type A compared to Type B subjects in control conditions is interpreted as reflecting a chronic disruption in attention functions for these individuals, possibly from internal distractions (self-instructed strategies to facilitate response speed, covert verbalizations about performance success, and the like). The possibility that the determination of Type A shape (less than 6μV for Cz in the relative difference in voltage values between points H and L in Fig. 1) was associated with CNV amplitude values of less than 6 μV appears unlikely in view of the comparable proportion of Type A and Type B individuals having Cz amplitude values above and below 6 μV. The pattern of relatively greater reduction in CNV amplitude by Type B subjects in the letters-recall task suggests that they may be more reactive to external distraction (letters) than Type A subjects. If these interpretations have any merit, it is possible that Type A subjects are more chronically distracted by internal sources and Type B subjects by external factors. The possibility that chronicity-reactivity differences in distraction characterize individuals classified by CNV shapes having fast and slow rise time deserves further study.

Summary

Twenty-four normal volunteers were tested in three conditions: (1) a constant-foreperiod simple reaction time task consisting of a flash-tone-key press sequence (control), (2) the same task with the addition of a short-term memory task consisting of four visual letters presented within the flash-tone interval with the requirement that they be repeated after the key press to tone (letters-recall), and (3) the presentation of letters without the requirement of recall (letters-no recall). CNV amplitude was reduced in both the letter recall and no-recall conditions compared to control. Reaction time increased only in the recall condition. Decreased CNV amplitude associated with lengthened RT was interpreted as a CNV distraction effect. Individuals with a fast CNV rise time (Type A) showed a pattern of lowered CNV amplitudes and lengthened RTs and appear to be chronically distracted. Subjects with a slow CNV rise time (Type B) showed a trend toward reduced CNV amplitudes during the letters-recall task and appear to be reactive to external distraction. The pattern of CNV amplitude, heart rate, eyeblink, and RT seems to provide a useful index of psychological disturbance.

Acknowledgments

The assistance of Debbie Meinbresse, Jean Nigro, Gene Y. Chen, Mary Beth Boehner, Linda Fuss, Baiba Liepins, and Andrea Schoening is gratefully acknowledged.

PERSONALITY TRAITS AND ELECTROPHYSIOLOGICAL FACTORS DURING SENSORY CONDITIONING IN NORMAL AND PSYCHIATRIC POPULATIONS

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Sensory evoked (EP) and slow potentials (SP) may vary with individual personality traits (e.g., Callaway 1975). Shagass (1972) reported that somatosensory EP amplitude is inversely related to extraversion scores on the Maudsley Personality Inventory. Knott and Irwin (1968) found that stress and constitutional anxiety in combination depress CNV amplitude. Buchsbaum and Pfefferbaum (1971) distinguished two types of subjects on the basis of response to photic stimulation: visual EPs either increased (augmenter) or decreased (reducer) proportional to stimulus intensity. Tecce and Cole (1974) also observed divergent electrophysiological patterns associated with behavioral alertness or drowsiness in two groups of normal adults following amphetamine administration.

Dongier (1973a) suggested that contradictory reports of the relationship of aberrant CNV patterns and clinical diagnosis may be a consequence of imprecise diagnostic categories. In order to avoid this nosological pitfall, the present study was designed to assess the relationship of personality traits and electrophysiological patterns irrespective of psychiatric diagnosis. A sensory conditioning paradigm (Lelord et al. 1958, Begleiter and Platz 1969, Laffont et al. 1972) was used to minimize intersubject variability in normal and psychiatric populations.

Method

Subjects

Forty-one normal (females–28, average age–23 years) and 95 psychiatric patients (neurotic–55, psychopathic–19, psychotic–13, unclassified–8, females –90, and average age–30 years) were examined. Psychiatric subjects were outpatients or confined briefly in a psychiatric ward. All subjects were intelligent and cooperative enough to complete a personality questionnaire.

Questionnaire

Fifteen questions were selected from a 52-item personality inventory previously administered to 144 subjects (including 86 psychiatric patients). These questions represented 15 personality traits derived from a principal component factor analysis. Three choices were possible for each question: 0=no response; 1=false; 2=true.

Neurobehavioral procedures

Subjects were isolated in a dark, soundproof room and sat in a comfortable armchair. Electrodes were placed at the vertex and occipital region referred to the left earlobe. EEG was recorded with ac amplifiers set at a bandpass down 3 dB between 0.1 and 100 Hz (cf. Lelord et al. 1976). Vertical and horizontal EOGs were also recorded.

Auditory and visual stimuli described by Laffont et al. (this volume) were used for sensory conditioning. Subjects completed two 1-hour sessions consisting of 10 series of 20 trials presented at random intervals varying from 4 to 30 sec. The auditory stimulus was presented alone during the initial two series of the first session to establish unpaired control values. A visual stimulus was presented 700 msec after the auditory stimulus during conditioning (eight series per session). The auditory stimulus was again presented alone during the final two series of the second session to study extinction of the conditioned response.

Data analysis

Signal averages were constructed for each series of 20 trials. Records were discarded if EOG deflections exceeded 8 μV. Electrophysiological and clinical data were then factor analyzed as described by Laffont et al. (this volume).

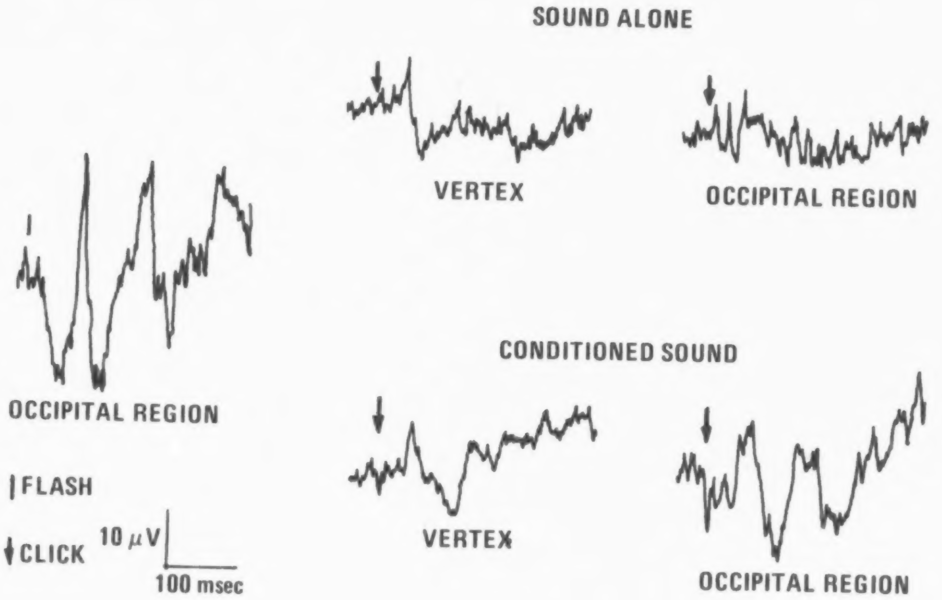


Fig. 1. Rhythmical potential conditioning. Each tracing represents average of responses to 20 stimuli. Left: visual evoked potential. Right: auditory evoked potential before conditioning (upper traces) and during conditioning (lower traces).

Results

Electrophysiological data

Fig. 1 to 3 illustrate three basic electrophysiological patterns observed during sound-light (SL) conditioning relative to sound alone (S) control waveforms. These patterns may be characterized as:

1. Rhythmic potentials associated with increased amplitude of the auditory evoked potentials (AEP) in the occipital region (Fig. 1).
2. Increased AEP amplitude at the vertex (Fig. 2).
3. Slow potentials (SP) at the vertex and/or occipital region (Fig. 3).

Evoked or rhythmical potentials within 400 msec of stimulus onset were counted if peak-to-peak amplitide was $\geq 4\ \mu V$. Slow potentials, measured relative to a 100-msec poststimulus baseline, were counted if the amplitude was $\geq 8\ \mu V$. The frequency (n) of occurrence of each pattern within the 16 conditioning series was classified as: *absent* ($n < 2$); *few* ($2 \leq n \leq 6$); *many* ($7 \leq n \leq 11$); or *great many* ($n \geq 12$). AEP amplitude was characterized as *large* if it exceeded control amplitude during either conditioning session, or *small* if it equaled control amplitude.

Visual evoked potentials (VEP) were classified separately as *moderately regular* ($6 \leq n \leq 12$) or *very regular* ($n > 12$) with *small* ($\leq 19\ \mu V$) or *large* ($\geq 19\ \mu V$) amplitude. VEPs were sometimes followed by rhythmic aftereffects. "Conditioning to time," defined as a response to "the absence of light," was sometimes observed during extinction series.

Factor analysis

Fig. 4 illustrates the results of factor analysis. Four factors emerged, represented as horizontal bands with characteristic electrophysiological (left) and psychological (right) features. Factors I and IV clearly reflected opposite extremes in terms of both electrophysiological measures and personality traits. These factors may be summarized as follows:

I. Trust and tolerance associated with rhythmic conditioning predominant occipitally without SPs.
II Reflection and stability associated with large conditioned EPs.
III. Restlessness associated with few conditoned EPs.
IV. Distrust and intolerance associated with localized or generalized SPs without rhythmic or conditioned EPs.

Discussion

Factor I was characterized by conditioned rhythmic and evoked potentials in the occipital region.

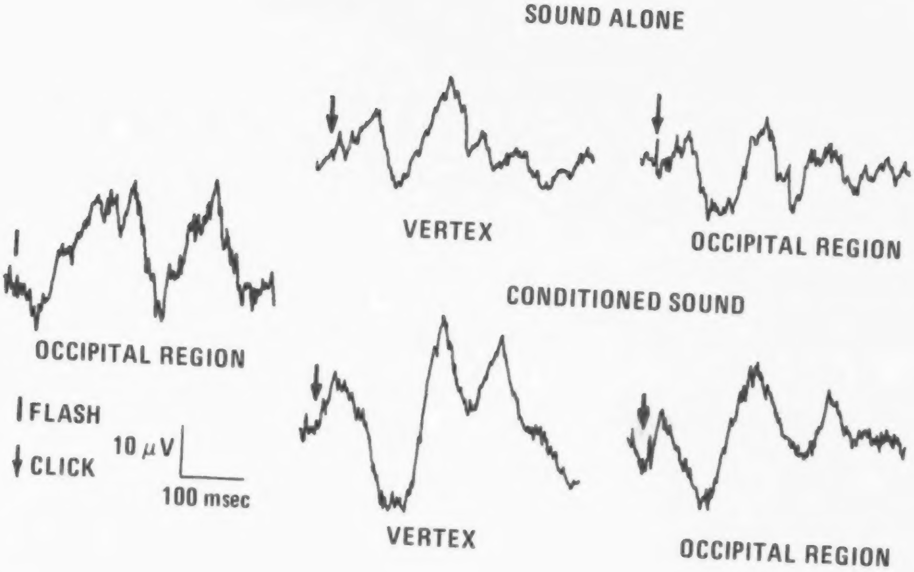


Fig. 2. Evoked potential conditioning. (See legend in Fig. 1.)

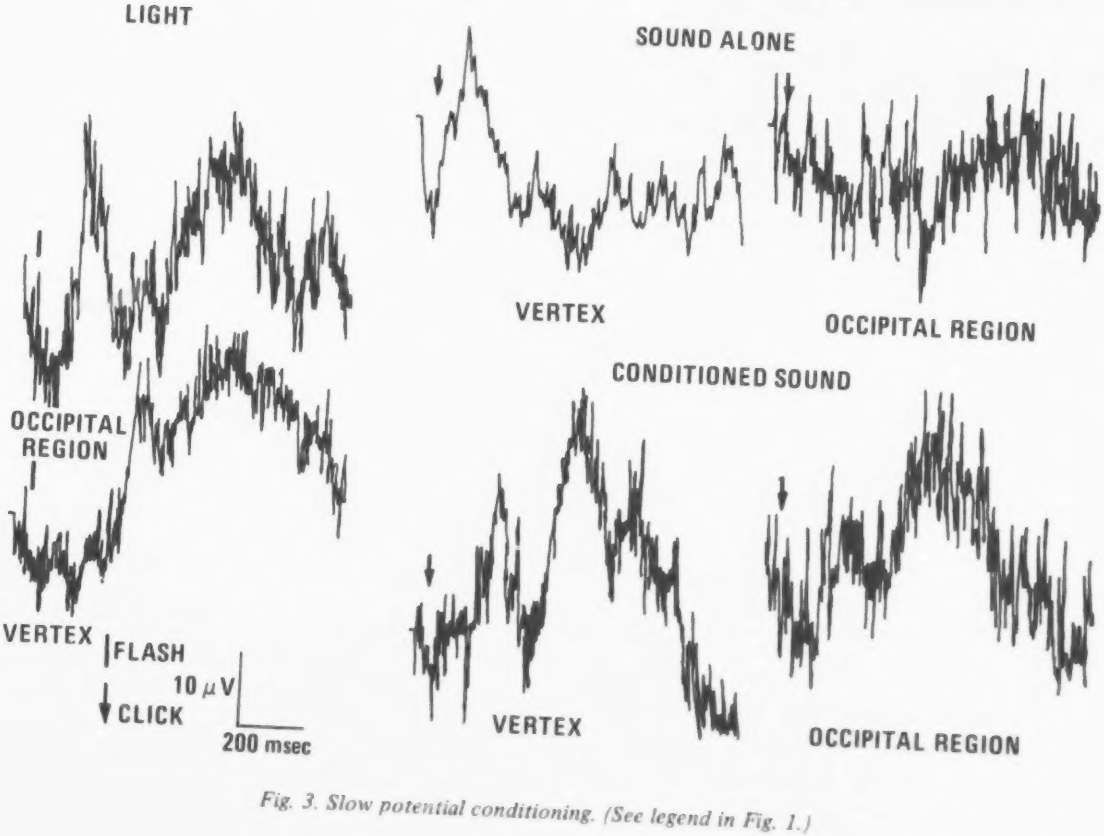
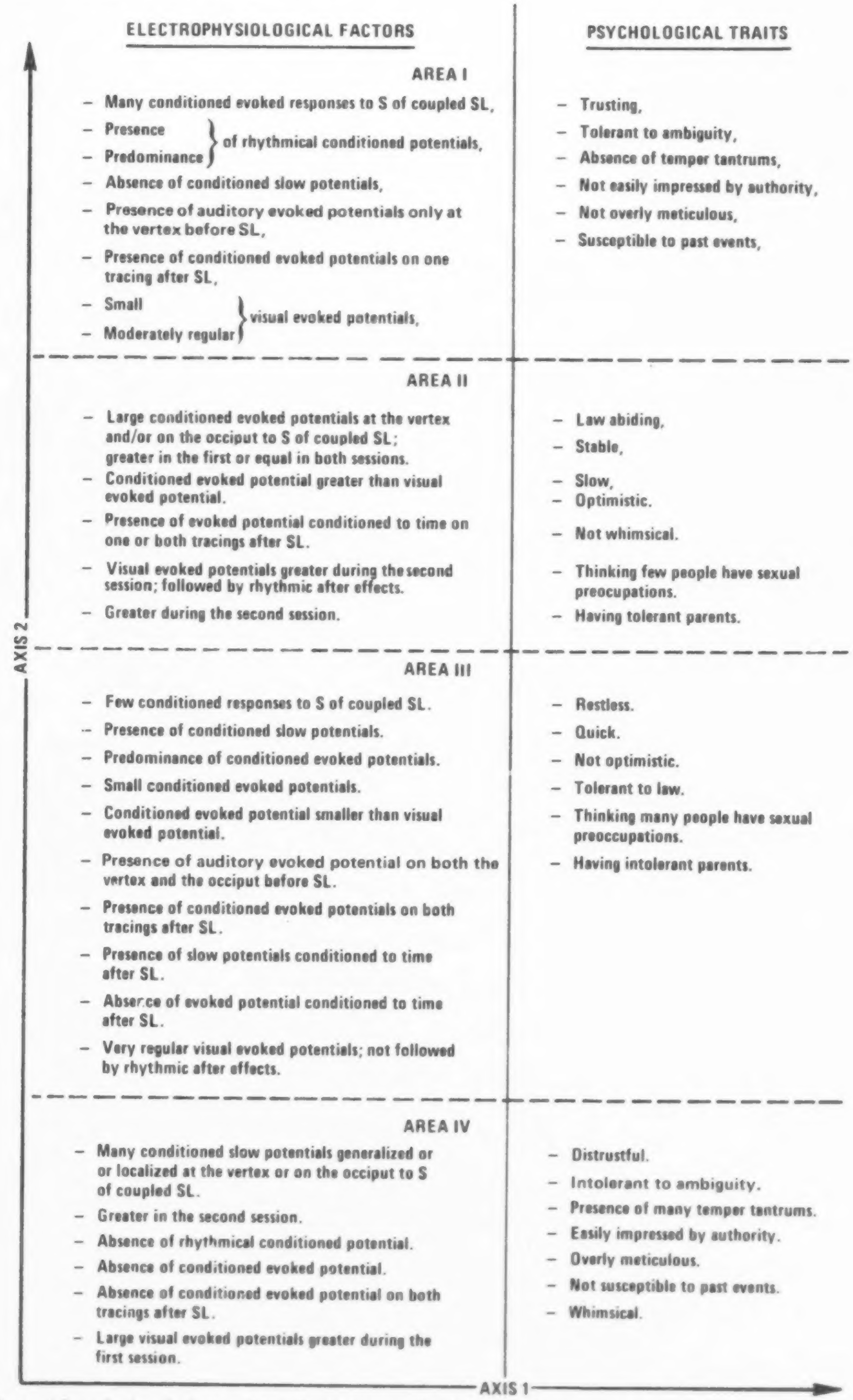


Fig. 3. Slow potential conditioning. (See legend in Fig. 1.)



	ELECTROPHYSIOLOGICAL FACTORS	PSYCHOLOGICAL TRAITS
AREA I	– Many conditioned evoked responses to S of coupled SL, – Presence – Predominance } of rhythmical conditioned potentials, – Absence of conditioned slow potentials, – Presence of auditory evoked potentials only at the vertex before SL, – Presence of conditioned evoked potentials on one tracing after SL, – Small – Moderately regular } visual evoked potentials,	– Trusting, – Tolerant to ambiguity, – Absence of temper tantrums, – Not easily impressed by authority, – Not overly meticulous, – Susceptible to past events,
AREA II	– Large conditioned evoked potentials at the vertex and/or on the occiput to S of coupled SL; greater in the first or equal in both sessions. – Conditioned evoked potential greater than visual evoked potential. – Presence of evoked potential conditioned to time on one or both tracings after SL. – Visual evoked potentials greater during the second session; followed by rhythmic after effects. – Greater during the second session.	– Law abiding, – Stable, – Slow, – Optimistic. – Not whimsical. – Thinking few people have sexual preoccupations. – Having tolerant parents.
AREA III	– Few conditioned responses to S of coupled SL. – Presence of conditioned slow potentials. – Predominance of conditioned evoked potentials. – Small conditioned evoked potentials. – Conditioned evoked potential smaller than visual evoked potential. – Presence of auditory evoked potential on both the vertex and the occiput before SL. – Presence of conditioned evoked potentials on both tracings after SL. – Presence of slow potentials conditioned to time after SL. – Absence of evoked potential conditioned to time after SL. – Very regular visual evoked potentials; not followed by rhythmic after effects.	– Restless. – Quick. – Not optimistic. – Tolerant to law. – Thinking many people have sexual preoccupations. – Having intolerant parents.
AREA IV	– Many conditioned slow potentials generalized or or localized at the vertex or on the occiput to S of coupled SL. – Greater in the second session. – Absence of rhythmical conditioned potential. – Absence of conditioned evoked potential. – Absence of conditioned evoked potential on both tracings after SL. – Large visual evoked potentials greater during the first session.	– Distrustful. – Intolerant to ambiguity. – Presence of many temper tantrums. – Easily impressed by authority. – Overly meticulous. – Not susceptible to past events. – Whimsical.

Fig. 4. Factorial analysis of relationships. Each electrophysiological factor was situated in relation to psychological traits. Each psychological trait was situated in relation to electrophysiological factors. The two spaces were projected on a two-dimensional space. A progression for electrophysiological factors as well as for psychological traits was seen along Axis 2.

This electrophysiological pattern implies conditioning with early latent responses and complex morphology in primary sensory cortex corresponding to the *unconditioned* stimulus (Lelord and Maho 1969). The electrophysiological-psychological structure of Factor I is reminiscent of the concept of "epicritic" sensitivity proposed by Head (1920). The traits of emotional between the psychological and electrophysiological domains. Laffont et al. (this volume) illustrate the use of this technique in the study of developmental distability and confidence are consistent with the pleasant sensibility of the epicritic mode.

Conversely, Factor IV reflected a different type of conditioning characterized by the absence of rhythmic or early evoked potentials, but the presence of diffuse late slow waves at the vertex and occipital area. This pattern represents global facilitation corresponding to the "protopathic" mode of Head. The traits of emotionality, instability, anxiety, and intolerance are also consistent with the unpleasant sensations attributed to protopathic function.

Although the present study is preliminary, the results provide encouraging evidence of a systematic relationship between personality trait structure and characteristic electrophysiological patterns. Furthermore, factor analytic techniques appear to provide an effective method to elaborate the complex relationship orders. These findings suggest that the search for electrophysiological correlates of psychopathology may be more fruitful if investigators focus on discreet measures of personality traits rather than diffuse, ill-defined diagnostic categories.

Summary

The relationship between evoked potentials and personality traits was examined in 95 psychiatric and 41 control subjects during sensory conditioning. Two major electrophysiological groups were distinguished by localized conditioned evoked potentials and generalized slow conditioned potentials. Epicritic evoked potential patterns were associated with emotional control, while protopathic slow potential patterns were associated with emotional prevalence.

CONTINGENT NEGATIVE VARIATION IN PATIENTS AFFECTED BY SPECIFIC PHOBIAS

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The essential clinical feature of phobic neurosis is the anticipatory fear of certain objects and situations. The anticipatory component of the phobia seriously disrupts the patient's life (Marks 1969). Research has focused on experimentally created anxiety rather than actual phobic states observed in patient populations. Measures of experimentally induced fear include: skin conductance (Ladar 1967, Wilson 1967), forearm blood flow (Kelly and Walter 1968), biochemical parameters (Marks 1969), and muscle activity changes (Malmo and Davis 1951).

Reduced CNV amplitude has been reported in anxiety situations (Knott and Irwin 1968, 1973; McCallum and Walter 1968). Knott and Irwin (1968) examined CNV and galvanic skin response (GSR) in subjects divided into high and low anxiety groups on the basis of scores on the Bendig Scale of Emotionality. No differences were observed between groups under normal conditions, but smaller CNV amplitudes were observed in the high anxiety group than in the low anxiety group under stressful conditions. GSR did not vary between groups; however, using a clinical model, where response differences between patients and normal controls or between responses to different stimuli in the same patient were evaluated, Wilson (1967) was able to show differences in GSR between phobic and nonphobic subjects.

The seeming discrepancy in results suggests that reactions of normal subjects to experimentally produced fearful situations may not be comparable to clinical conditions such as phobic neuroses. These results also point to the need to distinguish between the emotional experience of anticipatory anxiety and those somatic, visceral, and cognitive reactions to fear that are most likely related to different aspects of central nervous system activity.

CNV studies employing prolonged foreperiods (4 or more sec) have demonstrated that different processes contribute to the development of the CNV (Weerts and Lang 1973, Klorman and Bentsen 1975, Loveless and Sanford 1975, Rohrbaugh et al. 1976). Weerts and Lang (1973) suggested that anticipation of the imperative stimulus is important in generation of CNVs. Weinberg (1975) has argued that CNV development corresponds to the expectancy to receive rather than respond to information.

Anticipatory processes appear to play a central role in the etiology of phobic neuroses as well as the CNV. The CNV, therefore, should provide a sensitive index of the electrocortical effects of phobic neuroses as well as provide a prognostic index of therapeutic efficacy. In the present study, nondisturbing and phobogenic stimuli were used to study the CNV in phobic patients prior to and following desensitization therapy.

Method

Subjects were 14 female out-patients ranging in age from 21 to 50 years and suffering from phobias concerning dogs, spiders, bees, snakes, birds, frogs, and dolls. Subjects had an average phobic anxiety score of 2.8 and average avoidance score of 3.0 on a 0-4 scale questionnaire (Solyom et al. 1973). Average scores on the IPAT Anxiety Scale (Cattell 1963) and Fear Survey Schedule (FSS) Wolpe and Lang 1964) were 4.9 (normal is between 5 and 7) and 53.6 (normal is approximately 50), respectively.

All subjects participated in two recording sessions a week apart. The first allowed them to become acquainted with the procedure and sequences of the test. The second provided the data to be used in analysis.

The experimental paradigm used to elicit the CNV consisted of a warning click (S1) followed after 1.5 sec by a slide-projected picture (S2), which the subject terminated by pressing a button. Three series of stimulus pairs were presented. A nondisturbing picture was used as the imperative stimulus in the first and third series, and a picture of the feared object served as S2 in the middle section. ISI varied from 20 to 60 sec. Ten sweeps free of eye or skin potential contamination were summated for each series. The ratio of sweeps accepted varied in the population studied from half to one quarter of the trials presented.

Recording methods have been detailed elsewhere (Dubrovsky et al. 1973). Briefly, EEG was recorded at Cz using nonpolarizable Ag/AgCl electrodes referred to linked earlobes. The EEG preamplifier was modified to provide a 9.5-sec time constant with a 75-Hz upper frequency limit. Eye movements (EOG) were monitored with a supraorbital electrode referred to linked earlobes. Skin potentials were monitored by recording bipolarly between the two mastoids. EEG, EOG, and skin potentials were summated on line with a Mnemetron CAT 400A.

CNV amplitude was measured as the largest negative peak during the S1-S2 interval relative to a pre-S1 baseline. The baseline was set as the mean amplitude of a 1.5-sec epoch preceding S1. Duration of postimperative negative variation (PINV) was measured as the time between S2 and return of negativity to the baseline (Dongier 1973b). T-tests for dependent samples were used for statistical comparisons.

Results

Representative CNV patterns observed in patients in anticipation of disturbing and phobogenic stimuli are shown in Fig. 1 and 2. RT was shorter [t (13) = 2.92, p < .02] while CNV amplitude [t (13) = 6.48, p < .01] and PINV duration [t (13) = 2.92, p < .02] were greater for disturbing than nondisturbing stimuli (Table 1). No significant differences were noted between series one and three when nondisturbing stimuli were used.

Following the training and recording sessions, a group of the patients underwent desensitization therapy until symptomatic improvement was observed. Six subjects, who successfully concluded desensitization treatment, were tested again with nondisturbing and with phobogenic stimuli. CNV averages were obtained again for the two conditions: Fig. 2 (lower traces) shows CNVs obtained in the posttherapy session. In all six cases, no differences were observed in anticipation of nondisturbing compared to previously phobogenic stimuli. Two other subjects who had successfully completed their desensitization therapy were not available for posttherapy testing. Six subjects did not complete therapy.

Table 2 presents the pre- and posttherapy scores for the subgroup of treated subjects. Statistical analysis showed that following desensitization, CNV amplitude and PINV duration for phobogenic stimuli were reduced in comparison to pretherapy levels [t (5) = 5.2, p < .01 for amplitude; t(5)=2.12, p < .05 for duration].

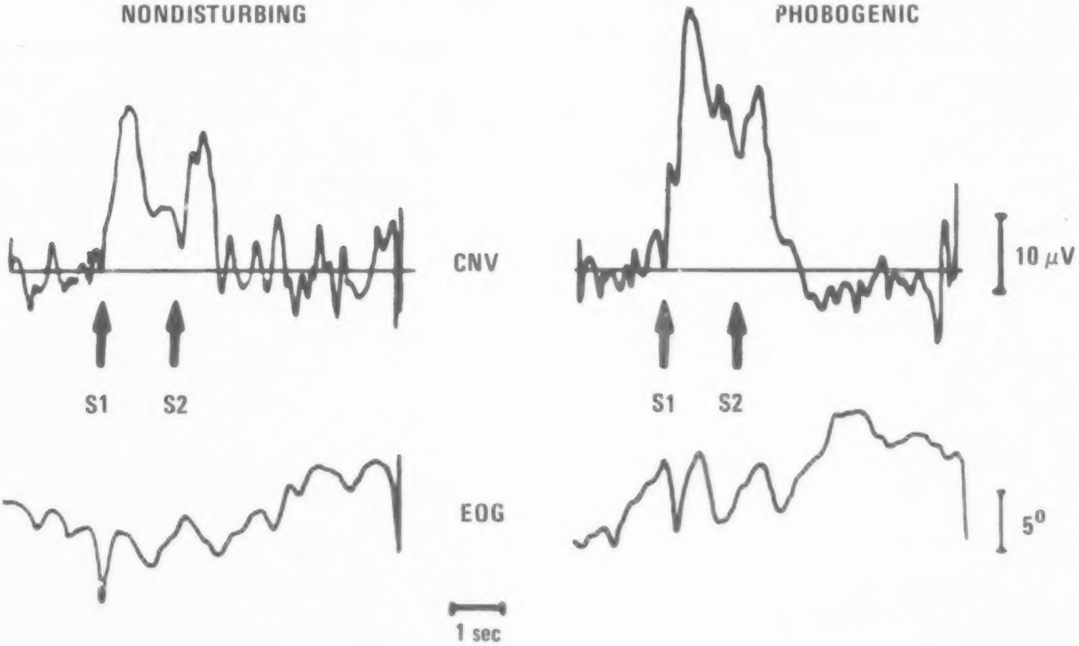

Fig. 1. CNV samples representative of the responses obtained from patients affected by specific phobias with presentation of nondisturbing and phobogenic stimuli.

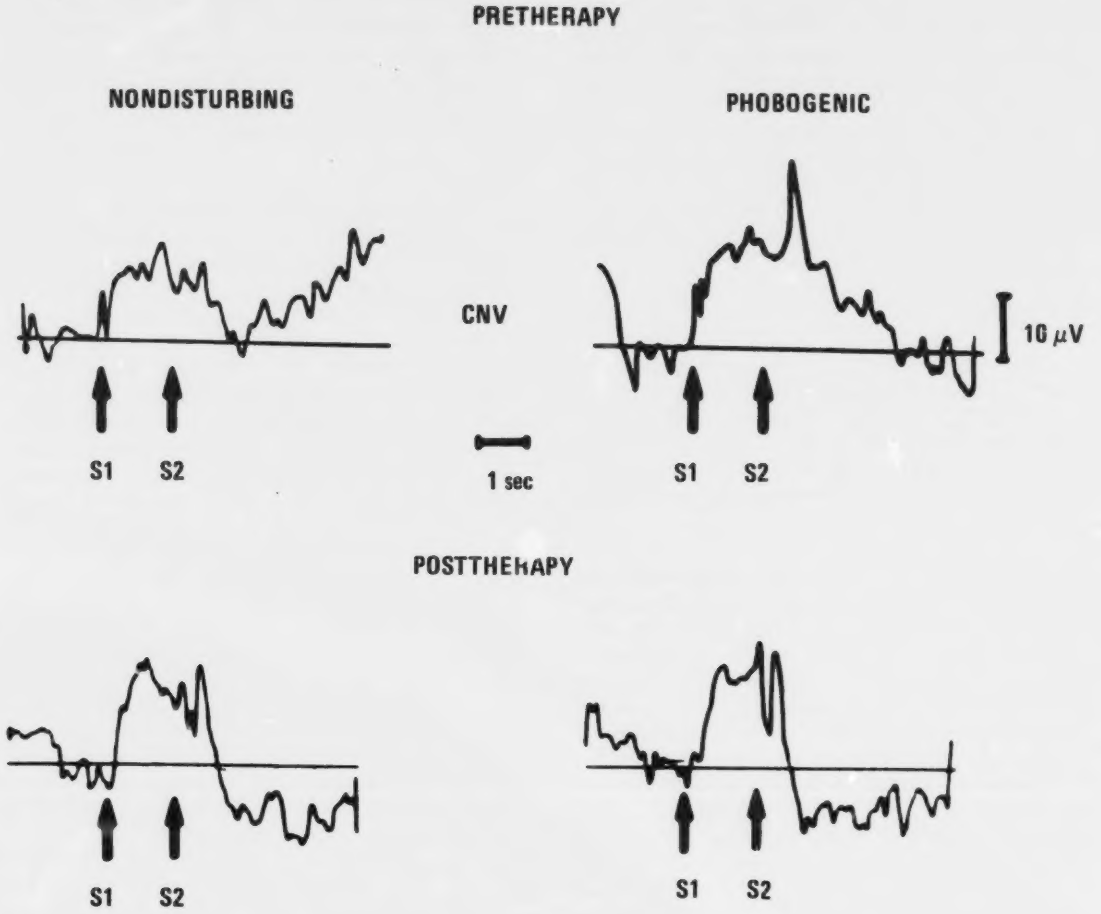

Fig. 2. Comparison of CNV samples in response to nondisturbing and phobogenic stimuli obtained from patients affected by specific phobias before and after treatment.

Table 1. Mean Values of CNV Amplitude, Duration and Reaction Time

	Amplitude, μV	Duration of negativity after S2, msec	Reaction time after S2, msec
Nondisturbing stimuli	11.3	1900	907.2^a
Phobogenic stimuli	20.4^b	2300^a	711.0

[a] t-test results: N=14, df=13, $p < .02$, two-tailed.

[b] $p < .01$.

Table 2. Mean Values of CNV Amplitude Duration, and Reaction Time before and after Desensitization Therapy

	Before therapy	After therapy
Nondisturbing stimuli		
Amplitude, μV	17	16
Duration, msec	1966	1833
Reaction time, msec	1043^a	850
Phobogenic stimuli		
Amplitude, μV	28^a	16
Duration, msec	2925^b	1858
Reaction time, msec	735	977

[a] t-test results: N=6, df=5, $p < .01$, one-tailed.

[b] $p < .05$

Behavioral and psychological test results also indicated a normalization of scores following therapy. RT increased slightly to phobogenic stimuli while the relatively long pretherapy RTs to nondisturbing stimuli were reduced [t (5) = 3.7, $p < .01$]. Statistical comparison of pre- and posttherapy psychological tests showed scores were reduced to normal values after completion of therapy [t (5) = 6.34, $p < .01$ for phobic anxiety; t (5) = 5.41, $p < .01$ for avoidance; t (5) = 2.5, $p < .05$ for IPAT (STEN); and t (5) = 2.5, $p < .05$ for FSS].

Discussion

The results demonstrate that CNVs from phobic patients are significantly larger and PINVs more prolonged when imperative stimuli depict phobogenic rather than nondisturbing stimuli. These differences may be attributed to the presumed importance of anticipatory processes in the etiology of phobic neuroses and the CNV.

Sharply rising high-amplitude negative shifts and prolonged PINVs following the warning stimuli were observed in phobic patients (cf. Fig. 1) when the paradigm contained phobogenic stimuli. According to Weerts and Lang (1973) and Loveless and Sanford (1975), the early negative phase of the CNV is related to signal stimulus orientation although the results of Rohrbaugh et al. (1976) are not consistent with this hypothesis. Loveless and Sanford suggest that the warning signal affects the gain of the threshold mechanism rather than its trigger level, i.e., the warning stimulus modulates the effective intensity of the imperative stimulus. These authors also showed that warning signal intensity affects the response characteristics for at least 8 sec after imperative stimulus onset. Perhaps the conditioned emotional significance of a stimulus modulates response threshold in a manner similar to physical intensity, an hypothesis that could account for the increased amplitude and prolonged duration of PINV observed in patients when the imperative stimulus was phobogenic.

The results may also be related to the compulsive search of phobic patients for the feared object (Marks 1969). A signal warning of the temporal proximity of the feared stimulus should produce a large orienting response and hence an orienting cerebral wave of large amplitude and duration. Similarly, the attentional process "which facilitates the selection of relevant stimuli from the environment" (Tecce 1972) should be enhanced while the patient searches for the feared object. According to Tecce's hypothesis, attention is positively and monotonically related to CNV amplitude. Differential CNV amplitudes and reaction times in the phobogenic versus nondisturbing conditions are consistent with this hypothesis.

Patients with specific phobias showed low levels of general anxiety consonant with the Maudsley study (Marks 1969). CNVs of this population were larger in amplitude when phobogenic stimuli compared to nondisturbing stimuli were used. These results and other reports of low CNV amplitudes in high anxiety subjects reveal that CNV amplitude can provide an objective indication of specific behavioral states, such as fear and anxiety. Furthermore, these electrophysiological results support the clinical view that fear, anxiety, and phobia encompass distinctive phenomena (Marks 1969).

Finally, CNV differences observed with phobogenic and nondisturbing stimuli disappeared in six patients after successful desensitization therapy, while responses to nondisturbing stimuli remained stable. These results suggest that changes in brain processes associated with phobic neuroses are reversible. Available data do not indicate whether amplitude and duration differences with phobogenic and nondisturbing stimuli involve changes in magnitude in the same CNV generators, or whether phobogenic stimuli activate other central nervous system areas specifically related to the pathological phobic condition.

In conclusion, we propose that sequential CNV evaluation during and after treatment may be used as an objective indicator of the treatment course in specific phobic neurosis. By comparing behavioral norms of improvement with CNV recordings, a better prediction of relapses may become possible, which may allow for the development of appropriate prophylactic measures, an important goal in psychiatric management.

Acknowledgments

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RELIABILITY OF CONTINGENT NEGATIVE VARIATION IN PSYCHOPATHOLOGY

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The reliability of a clinical testing procedure is an important point in determining its usefulness. With the CNV, however, the measurement of reliability in normal subjects has raised problems. While Cohen (1969) and Roth et al. (1975) obtained a high correlation between two CNV recordings, Straumanis et al. (1969) reported a low correlation. These differences might result from two important independent variables in test-retest studies: (1) the number of trials selected for averaging by different investigators (10 to 36) and (2) the time interval between successive recording sessions (5 minutes to 8 days). In psychopathology, a third variable is added: the possible change of the mental state of the patients. The present study was undertaken to determine the reliability of CNV recording across two different test-retest intervals (1 month and 1 year) and with two different–but complementary–psychopathological conditions (with improvement or aggravation of mental state).

Methods

One-hundred-six male subjects were selected on the basis of psychopathological history and psychiatric interviews from the 300 patients of the psychiatric hospital at La Voliere, Liege (mean age, 32 years; S.D., 4.52). The distribution of patients according to classical diagnostic categories is shown in Table 1. The frequency distribution is broken down in terms of patients who showed no change (N=76), who improved (N=24), and who deteriorated (N=6) during the test-retest period.

Two selection criteria were used: (1) patient cooperation in EEG and CNV recorded and (2) the presence of the behavorial disorder for at least 1 year. All patients received psychotropic medications.

In order to study CNV reliability among patients with stable behavior disorders, two recordings were made for each of 76 chronic patients. The test-retest interval was 1 to 2 months for half the patients and 1 to 2 years for the other half. No important clinical changes were reported in any of these subjects during an observation period of 2 weeks before and after recording sessions.

In order to study CNV reliability among patients who showed important changes in clinical state, CNVs were recorded from 30 chronic patients using a test-retest interval of 1 to 2 years: 24 displayed clear symtomatic improvement; 6 showed an aggravation of mental state.

EEG was recorded at Cz from Ag/AgCl electrodes referred to linked earlobes. EOG was recorded from

Table 1. Frequency Distribution of Patients According to Classical Diagnostic Categories and Clinical Change During Test-Retest Period

	No change	Improved	Deteriorated
Hebephrenic schizophrenics	21	1	3
Paranoid schizophrenics	27	18	0
Paranoics	7	0	0
Manic-depressives	9	5	2
Personality disorders	5	0	0
Obsessional neurotics	7	0	1
Totals	76	24	6

Table 2. Frequency Distribution of CNV Resolution Modes for Test-Retest Interval of 1-2 Years for 38 Patients with Stable Symptomology[a]

Second recording	First recording		
	Type I CNVs	Type II CNVs	Type III & IV or flat CNVs
Type I CNVs	6	1	2
Type II CNVs	2	0	0
Type III & IV or flat CNVs	2	1	24

[a] Test-retest correlation (Goodman-Kruskal Index) = 0.882

Table 3. Frequency Distribution of CNV Resolution Modes for Test-Retest Interval of 1-2 Months for 38 Patients with Stable Symptomology[a]

Second recording	First recording		
	Type I CNVs	Type II CNVs	Type III & IV or flat CNVs
Type I CNVs	7	0	4
Type II CNVs	2	2	6
Type III & IV or flat CNVs	1	0	16

[a] Test-retest correlation (Goodman-Kruskal Index) =0.784.

Table 4. Frequency Distribution of CNV Resolution Modes of 30 Patients Showing Distinct Symptom Change During the 1- to 2-Year Interval Between Recording Sessions[a]

Second recording	First recording		
	Type I CNVs	Type II CNVs	Type III & IV or flat CNVs
Type I CNVs	1[b]	2[c]	15[b]
Type II CNVs	1[d]	0	7[b]
Type III & IV or flat CNVs	3[d]	0	1[d]

[a] Test-retest correlation (Goodman-Kruskal Index) = -0.56

[b] Improved.

[c] One improved; one deteriorated.

[d] Deteriorated.

above and below the right eye. Both signals were recorded with a time constant of 11 sec. Calibration signals of 20 μV were recorded in series with CNV and EOG leads on each trial. The data were stored on analog tape for off-line summation. Subjects were required to keep eyes closed during testing. Trials containing EOG artifact were rejected from averages.

The paradigm used for testing was a warning click (S1) followed after 1.5 sec by a series of light flashes (S2), which the subject terminated by pushing a button. The CNV was obtained by summating 20 trials.

Three CNV parameters were measured: pre-S2 amplitude, post -S2 duration, and resolution mode. Amplitude was defined as the difference in mean voltage between a 200-msec pre-S2 epoch and a 1-sec pre-S1 baseline epoch. Post-S2 duration was defined as the delay, in seconds, between S2 and the return to baseline of the CNV. In normal curves this delay is about 0.4 sec; in some patients, it ranges between 1 and 4 sec. Resolution mode is judged in relation to the four types of CNV identified previously (Timsit-Berthier et al. 1973): Type I-CNV returns to baseline immediately after S2; Type II-baseline return is delayed, although the drop begins immediately after S2; Type III- baseline return is delayed with no immediate drop after S2, i.e., the CNV remains at creases in amplitude after S2, which yeilds a characteristic dome-shaped curve.

The Bravais-Pearson Index (Kendall and Stuart 1967) was used to calculate test-retest correlations for amplitude and duration measures. The Goodman-Kruskal Index was used to correlate qualitative ordinal test-retest measures of CNV resolution.

Results

In the stable patient population, significant correlations ($p < .05$) for amplitude measures were obtained for test- retest intervals of 1 to 2 months (ρ=0.55). Test-retest correlations for the duration measure were significant only for the 1-to 2-year interval (ρ=0.44). The highest test-retest correlations were obtained for resolution mode ratings. The Goodman-Kruskal Index was 0.88 for the 1- to 2-year interval and 0.78 for the shorter interval. The frequency distributions of resolution modes obtained for the longer and shorter intervals are shown in Tables 2 and 3, respectively.

Table 4 shows the frequency distribution of resolution modes in 24 subjects exhibiting symptomatic improvements and in 6 subjects (2 manic-depressives, 3 acute schizophrenics, and 1 neurotic who had a hallucinatory episode) who deteriorated. These two populations were combined in order to test for the effect of absolute change in mental state during the 1-to 2-year test-retest interval. A significant positive correlation ($\rho=0.48$) was obtained for the amplitude measure; a significant negative correlation ($e=-0.56$) was obtained for resolution mode; but the correlation of the duration measure ($p=0.15$) was not significant.

Discussion

The test-retest reliability of three CNV parameters was examined in psychopathological patients. The most informative and reliable of these measures was the qualitative rating of resolution mode. This measure correlated positively for both short and long intervals in patients with stable symptomatology, but correlated negatively in patients who showed a distinct change in mental state during the 1-to 2-year-test-retest interval. This parameter appears to be a sensitive index of clinical change and, therefore, may be of prognostic value.

Acknowledgment

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CNV IN PATIENTS AFTER PSYCHOSURGERY AFFECTING THALAMOCORTICAL PATHWAYS TO PREFRONTAL CORTEX[1]

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This report examines the role of thalamofrontal pathways, including the anterior thalamic radiations, in the genesis of frontal CNV. The necessity of these connections for the production of prefrontal cortical negative slow potentials (SPs) elicited in cats during behavioral conditioning has been reported by Skinner and Lindsley (1973). Zappoli et al. (1973, 1976) observed normal frontal CNV in two patients treated with bilateral prefrontal lobotomy (Freeman and Watts 1939, 1947, 1950, 1966), which severed the thalamofrontal pathways. To shed further light on this problem, waveforms of frontal and vertex CNVs in patients subjected to various psychosurgical procedures were examined. These tractotomy procedures interrupted pathways originating in the dorsomedial and anteromedial nuclei of the thalamus projecting to various areas of prefrontal cortex.

Method

Eight nonschizophrenic patients (seven of whom were male), aged 37-74, were selected on the basis of fair neuropsychiatric condition and precise knowledge of lesions. The location and extent of lesions were determined by neuroradiological examinations (pneumoencephalography) and in two cases by computed tomography (Baker 1975, Baker et al. 1975). Psychosurgical history and present condition of each patient are summarized in Table 1.

An extensive bilateral prefrontal lobotomy using the classic "radical" plane of sectioning was performed on six patients (M47, M50, M53, M55, M56, and F74), 14-24 years ago ($\bar{X}$=18 years). This plane passes just rostral to the lateral ventricle anterior horn, cutting the greater part of the central white matter of the prefrontal areas, and interrupting intercommunications between thalamic dorsomedial nuclei and cortical areas 9, 10, 11, 13, 14, and 46 as mapped by Brodmann (1909, 1925). In these patients, insertion of the leucotome was extended with different techniques to the midline in an attempt to sever the more medial fibers connecting thalamic anteromedial nuclei and Brodmann's areas 24 and 32. In five patients, operation resulted in some improvement of phobias, obsessive thinking, compulsions, and emotional changes. One patient (F74) did not benefit from the operation. In five Ss there was no evidence that psychosurgery impaired I.Q., memory, imagination, or social attitudes, although distractibility increased noticeably in patients following surgery. One patient (M50) exhibited an intellectual deficit (Wechsler-Bellevue AIS I.Q. 85 and M.D.I. 60).

The seventh patient (M48), suffering from severe anxiety neurosis with episodes of intense agitation and depression, was treated by two successive psychosurgical operations. The first, performed 23 years previously, was a left frontal lobotomy with sure destruction of the dorsomedial thalamo-prefrontal fibers. The incision was on a plane so posterior that it produced a lesion of the lateral ventricle left frontal horn (documented with pneumoencephalogram). The patient's psychopathological condition remained unaltered, and he was treated a year later by a right extensive gyrectomy, with removal of the whole area 9 and upper half of areas 10 and 46 (Fig. 1). No neurological or intellectual deficits were apparent.

The last patient (M37), afflicted with a serious painful left lower phantom limb, had been subjected 2 years earlier to a right prefrontal chemical stereoleucotomy (alcoholization). This procedure generally causes well-delimited extensive lesions in the white matter of the prefrontal lobe with destruction of fibers originating in the thalamic nuclei, particularly in the dorsomedial and anteromedial. By means of computed tomography, this patient was found to have a roundish lesion of about 2.5-cm diameter a little below and about 1 cm in front of the right lateral ventricle anterior horn. In view of its extent and site, this lesion must certainly have caused interruption

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[2] Institute for Information Processing (IEI) of National Research Council (CNR), Pisa, Italy.

Table 1. Psychosurgical Patient History and Present Condition

Patient		Preoperative mental condition	Psychosurgical procedure	Years since operation	Present condition	Present anxiety level - STEN score[a]
Sex	Age					
M	55	Chronic high anxiety, obsessive-compulsive psychoneurosis	Freeman-Watts radical bilateral prefrontal lobotomy; lateral approach	24	Little improvement; no intellectual deficit	9
M	50	Chronic neurotic depression with anxiety and obsessive tendencies	Freeman-Watts radical bilateral prefrontal lobotomy; lateral approach	22	Little improvement; moderate intellectual deficit	6
M	47	Chronic high anxiety, obsessive-compulsive psychoneurosis	Freeman-Watts radical bilateral prefrontal lobotomy; superior approach	18	Significant improvement; no intellectual deficit	7
M	56	Chronic moderate anxiety, obsessive-compulsive psychoneurosis	Freeman-Watts radical bilateral prefrontal lobotomy; superior approach	15	Little improvement; no intellectual deficit	5
M	53	Chronic high anxiety, obsessive-compulsive psychoneuroris	Freeman-Watts radical bilateral prefrontal lobotomy; superior approach	18	Little improvement; no intellectual deficit	9
F	74	Chronic manic depressive psychosis with obsessive tendencies	Freeman-Watts radical bilateral prefrontal lobotomy; superior approach	14	No improvement; no intellectual deficit	8
M	48	Chronic severe anxiety psychoneurosis with episodic agitation or depressive states	1st left radical prefrontal lobotomy 2nd right gyrectomy of areas 9, 10, and 46.	23 22	Little improvement; no intellectual deficit	8
M	37	Left lower phantom limb pain	Right prefrontal chemical stereo-leucotomy	2	Transitory significant improvement; no intellectual deficit	7

[a] IPAT anxiety scale, R.B. Cattell (1963).

of pathways originating in the dorsomedial nucleus and projecting to right frontal areas 9, 10, 11, 13, 14, and 46.

All patients were capable of performing a typical CNV task, which was in this case a click warning stimulus (S1) followed after 1 or 1.5 sec by a tone imperative stimulus (S2) of moderate intensity. A button press, which S was instructed to make as fast as possible, terminated the tone (operant response). Eighty to 100 paired click-tone trials were presented, with a variable intertrial interval (ITI) ranging from 10 to 60 sec.

Ag/AgCl recording electrodes were applied at Cz, Fp2, Fp1, F4, F3, F2, and F1; the last two were centered equidistantly between, respectively, Fp2, F4 and Fp1, F3. Two methods of reference were used in a session: (1) Cz to linked earlobes and frontal electrodes to ipsilateral mastoid and (2) all electrodes to linked mastoids. Also recorded were vertical EOG, finger photoplethysmogram, the EMG of forearm flexor muscles involved in the operant response, stimulus markers and reaction times (RT) to S2. EEG and V-EOG were recorded using a 6-sec TC. Data were stored by an FM tape recorder for off-line analysis

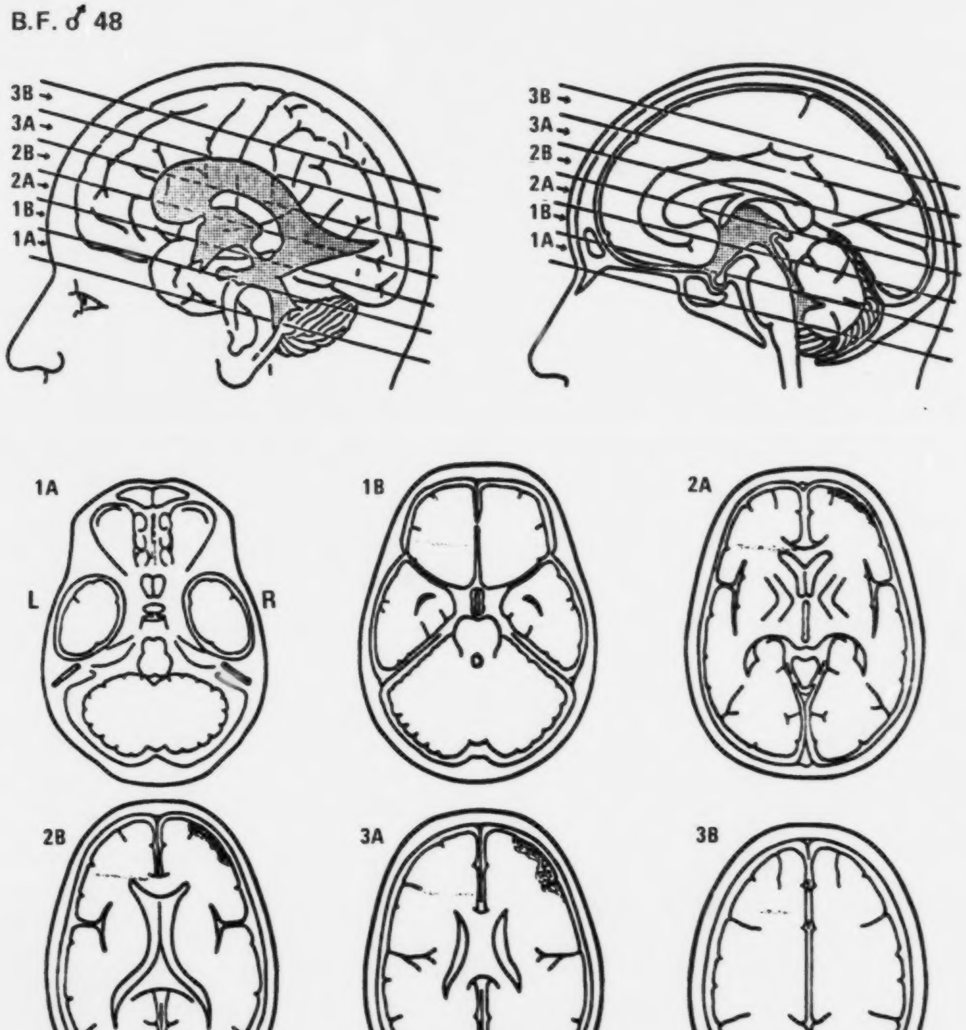

Fig. 1. Computed tomography of patient M48. Quite visible lesion produced by left frontal radical lobotomy and the result of right prefrontal extensive gyrectomy (probably the whole of Brodmann's area 9 and upper half of areas 10 and 46).

by a general-purpose computer. Relatively artifact-free 5-sec EEG epochs were averaged with 8 or 16 trials in an average. CNV amplitude was quantified in terms of the excursion from baseline at 200, 150, and 100 msec preceding S2. Baseline was defined as the average amplitude of EEG activity occurring 800 msec preceding S1. Methods are described in detail elsewhere (Zappoli et al. 1973).

Results

CNV, postimperative negative variation (PINV), and RT measures for each patient and for a control group of 10 volunteer Ss are reported in Table 2. CNVs recorded in patients were slightly attenuated, especially in Ss with high anxiety levels, but negative deflections could consistently be elicited on the frontal thalamo-disconnected areas.

In one (M55) of the six patients treated by bilateral extensive "radical" prefrontal lobotomy, no ISI slow potential shifts were observed in any derivations. The patient responded repeatedly only to S2, and the response almost always coincided with the start of an ample PINV of about 1450-msec duration, present symmetrically over frontal areas and at the vertex. When questioned afterward, the patient, who was very tense, answered that he clearly noticed S1, but never considered it as a warning signal.

In the other patients of this group, fairly typical CNVs were elicited over frontal areas and at the vertex (Fig. 2). In three patients (M50, M53, and F74), slight frontal CNV asymmetries were observed in some averages (Fig. 2). These asymmetries were inconstant as to laterality, were without clinical or neuroradiological explanation, and were not enhanced by use of ipsilateral mastoid references—a method previously shown to accentuate asymmetries (Zappoli in press). In patients M50 and F74, frontal and vertex CNVs were often followed by an evident PINV (Fig. 2A, B), especially when Ss exhibited excessive emotional tension and were requested to avoid eye and head movements during trials.

Patient M48 had been treated by left frontal lobotomy and right extensive frontal gyrectomy (Fig. 1). At Cz and left frontal area, he presented CNVs of fairly normal features, but of low voltage, sometimes followed by a PINV. At Fp2 and F2 no CNV activity or PINV was observed (Fig. 3A). Only at F4, immediately behind the gyrectomized area, did low voltage CNVs and PINVs become observable (Fig. 3B).

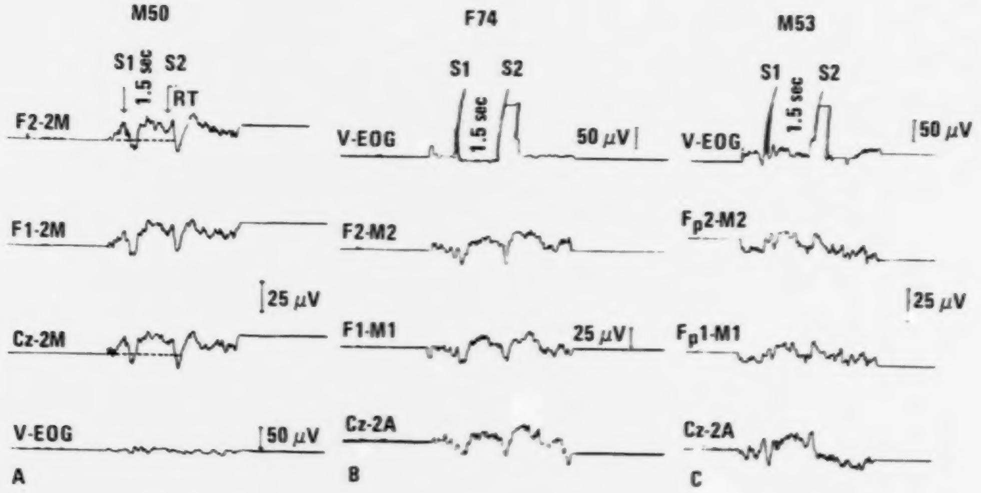

Fig. 2. CNVs showing moderate asymmetries. (A) Normal CNV followed by an evident PINV of about 1200-msec duration in prefrontal and vertex derivations. Mean RT about 280 msec. (B) CNV with attenuated amplitude and almost normal features, followed by an evident PINV of about 1300-msec duration, in prefrontal and vertex derivations. Mean RT about 410 msec. (C) CNV of normal shape but low amplitude in prefrontal and vertex derivations. Mean RT about 340 msec. In A, B, and C, moderate asymmetries of the prefrontal CNVs are observable. These asymmetries appeared, however, very irregularly as to side in different sets of eight trials and in these patients were apparently without clinical and neuroradiological explanation. Pre-S1 has 800-msec baseline, 5-sec total display time with negative up and TC of 6 sec.

Table 2. Slow Potentials and Reaction Time Measures

	CNV amplitude[a], μV									
Patient Sex Age	Fp2-2M	Fp1-2M	F2-2M	F1-2M	F4-2M	F3-2M	Cz-2M	Cz PINV duration,[b] msec	Reaction time,[c] msec	Range, msec
M 55	No CNV	No CNV	–	–	No CNV	No CNV	No CNV	1450	415	365-515
M 50	-10.1	-10.1	-11.2	-12	–	–	-15.4	1225	245	135-380
M 47	–	–	-9.9	-10	-11.6	-11.6	-15	No PINV	150	105-250
M 56	-10.4	-10.4	–	–	-13.2	-13.4	-17.6	No PINV	180	110-275
M 53	-7.2	-6.2	-8.6	-8.8	–	–	-11.2	No PINV	280	155-430
F 74	-9.1	-9.2	-10.8	-9.3	-10.6	-10.6	-11.8	1295	385	210-460
M 48	No CNV	-9.2	No CNV	-11.2	-9.4	-9.5	-12.6	1255	225	140-295
M 37	-7.2	-7.1	-8.3	-8.6	-7.2	-7.2	-13.1	No PINV	350	210-680
Mean ± (SD)	-8.8 (2.0)	-8.7 (1.9)	-9,8 (1.5)	-9.9 (1.5)	-10.4 (2.3)	-10.5 (2.3)	-13.8 (2.4)	1308 (119.3)	278 (136)	
Controls 10 Ss aged 24-39 Mean: 36.6					-12[d] (range: -6 to -17.9)	-11.8[d] (range: -6.2 to -17.5)	-25.6[d] (range: -19.5 to -36)	–	167.4[d]	88-235

[a] Mean of all sets of eight averaged trials; amplitude measured 200 msec prior to S2.

[b] Mean of all sets of eight averaged trials in which PINV was present.

[c] Mean of all trials selected for averaging.

[d] Mean CNV amplitudes and RT duration, with minimal and maximal values of all sets of eight trials selected for averaging in the entire group of controls. Zappoli et al. (1973).

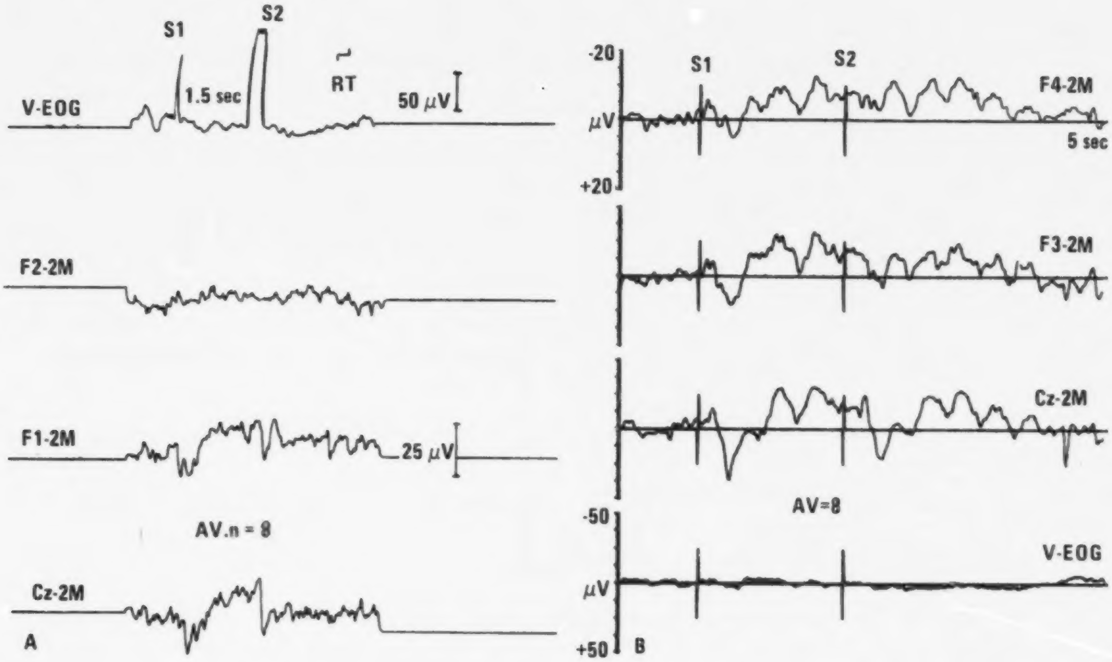

Fig. 3 CNV in M 48, the left frontal lobotomized and right frontal gyrectomized patient. (A) with F2-linked mastoids, CNV activity and PINV are absent. With other derivations (F2-M2, Fp2-2M, Fp2-M2), this absence was noted on the whole area of the right frontal extensive gyrectomy. Mean RT about 218 msec. (B) Low-voltage CNV followed by a PINV is present immediately behind the gyrectomized area (F4-2M). These SPs were easily elicited on all the other areas explored. Averages of eight artifact-free trials.

In the case of M37, who had been subjected to right extensive prefrontal stereoleucotomy, CNVs of low voltage were easily elicited from all areas explored (Fig. 4). These CNVs always reached maximum amplitude after S2, often with slow return to baseline.

In most patients, RT to S2 was fairly long. The mean RT of all trials selected for averaging in the entire group of patients was 278 msec (range: 105-680). RTs for each patient and control Ss are given in Table 2.

Discussion

These results show that it is possible to elicit frontal CNV even when the integrity of mediothalamic-frontocortical pathways is interrupted. These findings are inconsistent with observations by Skinner and his colleagues (Skinner 1971, Skinner and Lindsley 1973, Skinner and Yingling 1976) that cryogenic blockage in cats of the inferior thalamic peduncle (ITP) abolished surface negative SPs in the ipsilateral frontal cortex. On the basis of this evidence, Skinner has hypothesized that the mediothalamic-frontocortical biderectional system plays an important role in generating and regulating frontal negative SPs elicited by behavioral conditioning (cf. Skinner's neurophysiological model for the regulation of sensory input to cerebral cortex, this volume). The presence of frontal CNV in lobotomized patients is not easily explainable in terms of this model.

It is impossible on the basis of autoptic findings in lobotomized patients to sustain any regeneration of the sectioned mediothalamic prefrontal connections (Freeman and Watts 1947, 1966). The results reported here show that formation and regulation of prefrontal CNVs in humans may occur independently of the anatomo-functional integrity of communicating pathways to and from mediothalamic nuclei and anterior frontal cortex. CNV patterns in lobotomized patients suggest that the prefrontal cortical areas continue to receive and process information relevant to stimuli.

Possible explanations of frontal CNVs in lobotomized patients include:

1. Scalp electrodes, especially when referred to linked mastoids, may reflect ERPs from much wider cortical areas than those immediately underneath the electrodes. This possibility, however, would seem to be refuted by observations of patient M48, treated by

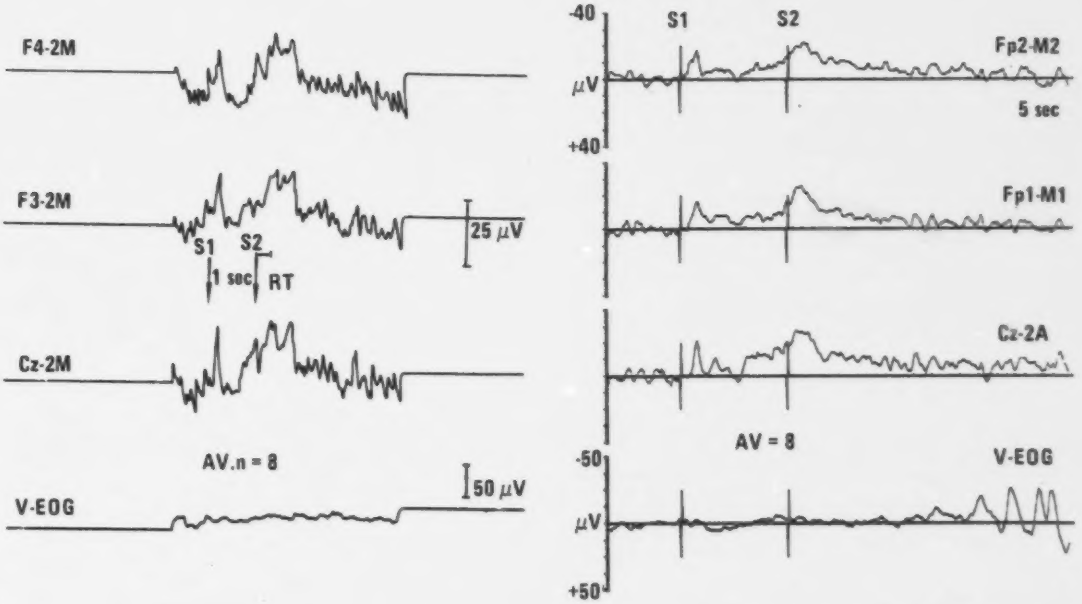

Fig. 4. CNV in M 37. Averaged potentials obtained with different electrode montages. 2M: linked mastoids: M1, M2: ipsilateral mastoids; and 2A: linked ears. Low-voltage CNVs were easily elicited from all explored areas, and negative shifts always reached maximum amplitude after S2, with slow return to baseline. Mean RT about 308 msec.

right frontal gyrectomy. No measurable CNV activity was observed over the ablated cortical area. Activity was observed immediately behind the gyrectomized area.

2. Transcortical mechanisms, i.e., tangential propagation of activity from distant cortical centers, may be involved in generating and regulating CNV in frontal cortex anterior regions, although there are no EP or neurophysiological data to unequivocally support this hypothesis. Ennever (1975), for instance, found no evidence for tangential transmission across the cortex in rats of the short-latency surface response evoked by weak somatic stimulation.

3. Frontal CNV generation and regulation in an operant conditioning situation may, in humans, be mediated by cortical and subcortical connections forming part of a diffuse, probably extrathalamic, projection system of which the exact source, distribution, and structure are presently unknown. Since CNV-like waveforms have been recorded at many locations along the neuraxis from brainstem to cortex, contingent negative variation may simply be an electrocortical sign of a general neuronal process occurring diffusely throughout the brain. This hypothesis would account for the present observations as well as the bilaterally symmetrical CNVs reported by Gazzaniga and Hillyard (1972) in "splitbrain" patients cued unilaterally to respond. Hillyard (1973), in fact, suggested that human CNVs contain a bilateral component activated by a nonspecific subcortical mechanism. Thus, neither bilateral thalamofrontal tractotomies nor transection of the forebrain commissures impairs the development or symmetry of premotor CNVs.

The method of cryogenic lesions (Skinner 1971) that transitorily abolishes frontal SPs probably influences cerebral structures other than the ITP and alters the state of consciousness, as manifested by behavioral changes. With respect to the cryogenic data, McSherry (1973) stated that "it is difficult to interpret these data in terms of an organism in a state of mind capable of generating a CNV."

4. It is also conceivable that unknown compensatory mechanisms could have produced new functional connections (other than the regeneration of severed pathways) during the 20 years since lobotomies were performed in these patients.

Each of these hypotheses requires further assessment in human and animal models.

Acknowledgments

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ABSENCE OF CNV REBOUND IN PSYCHOSURGERY PATIENTS[1]

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Event-related slow brain potentials are useful as neurophysiological indicators of information processing. For example, the development of contingent negative variation (CNV) (Walter et al. 1964) is disrupted and reaction time to S2 is lengthened (CNV distraction effect) when a unified attention set to S2 is disturbed by the imposition of a short-term memory task for letters presented in the auditory mode (Tecce et al. 1976) or for letters or numbers presented in the visual mode (Roth et al. 1975; Tecce et al., this section). In addition, the CNV distraction effect has recently been demonstrated with a short-term memory task in which trials including letters were randomly interspersed with trials having no letters (Tecce, this volume). An unexpected finding in the latter study was the significant elevation of CNV amplitude during the no-letter trials. This supra-normal magnitude of CNV was interpreted as a rebound function and as a possible index of plasticity in human brain functioning. In the present study, an attempt was made to assess the CNV rebound effect in psychosurgery patients.

Methods

Participants were 14 young normal volunteers (6 males and 8 females) aged 19 to 26 ($\bar{X} = 21.43$) and 19 psychosurgery patients (7 males and 12 females) aged 34 to 73 ($\bar{X} = 47.11$). Patients had received a bimedial prefrontal leucotomy (Valenstein 1973, p. 280) within a 12-year period prior to testing. In this procedure, medial fibers (white matter) connecting prefrontal cortex to thalamus are destroyed. With this technique, there is an expectation of a high degree of consistency in surgical lesions. No individual was an inpatient at the time of testing. Eighteen patients had a history of electroshock therapy and, at the time of testing, all patients were on medication including psychotropic and analgesic substances. Assessments of clinical status were made on the basis of interviews by two psychologists, a social worker, and a psychiatrist and by standardized rating procedures such as the Psychiatric Status Scale and Problem Appraisal Scale. Information on psychopathology will appear in a subsequent report.

The experimental task consisted of a constant-foreperiod simple reaction-time paradigm. The prepratory stimulus (S1) was a 150-msec flash of a black "X" on a circular patch of dim light 2.5 cm in diameter. The second stimulus (S2) was a continuous 1000-Hz tone of 70 dB (SPL) presented through earphones 1.5 sec after the "X" and terminated by a telegraph key press (KP). Intertrial intervals varied randomly from 8 to 14 sec ($\bar{X} = 11$) within a rectangular distribution of values 1 sec apart.

The two experimental conditions were "control" and "50% letters." The control condition consisted of 31 trials of the S1-S2-KP sequence and lasted 7 min. A second control condition after "50% letters" was omitted since previous work has shown no difference in CNV amplitude values between control conditions administered before and after letters (Tecce et al.

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[3] Research Scientist Awardee 5-K5-14915 from the National Institute of Mental Health.

1976; Tecce, this volume). The 50%-letters task consisted of 31 trials divided randomly into two types: letter trials and no-letter trials. No-letter trials and control trials were identical. Letter trials were similar to no-letter trials except that three successive letters were presented visually between flash and tone (within the S1-S2 interval) in a short-term memory task. Subjects were instructed to repeat aloud the three letters following key press. The letters were a random sample for each trial from the following: A, C, E, H, K, L, N, P, S, and U. The first letter appeared 50 msec after termination of S1; the interletter interval was 200 msec. Each letter lasted 200 msec. In the 50%-letters task, the first trial had no letters and was omitted from data analysis. The sequence of the remaining 15 letter trials and 15 no-letter trials was random and the same for all subjects.

Electroencephalographic (EEG) recordings were made from frontal (Fz), central (Cz), and parietal (Pz) scalp areas with linked earlobes as reference. A vertical electrooculogram (EOG) was recorded from above and below the right eye. Electrodes were Beckman Ag/AgCl standard (for EEG) and miniature (for EOG and reference) types. A Grass Model 7B polygraph was used to record EEG and EOG (time constant: 8 sec). High frequency cutoff was 75Hz (50% amplitude reduction with 12 dB/octave roll-off). EEG and EOG were recorded on magnetic tape to permit editing of artifact trials during off-line averaging with a CAT 1000. Averaged CNVs were based on 6 to 12 trials, the number being constant for a given individual. Trials with eye movement, including eyeblinks, or pre-S2 key presses were excluded from analysis.

Mean differences in CNV amplitude between patient and nonpatient groups were evaluated by independent *t* tests based on 31 df; units of analysis were either raw scores for control trials or difference scores (letter trials minus control trials and no-letter trials minus control trials). Within-group comparisons of both letter and no-letter trials with control trials were evaluated by correlated *t* tests based on 18 df (patients) and 13 df (non patients).

Results and discussion

Table 1 presents CNV amplitude values for letter, no-letter, and control trials of patient and nonpatient groups. Fig. 1 shows difference scores for CNV amplitudes recorded at Fz, Cz and Pz sites of patient and nonpatient groups. Examples of CNV tracings for a patient and a nonpatient appear in Fig. 2.

As shown in Table 1 and Fig. 1a, CNV amplitude was significantly lower in letter trials than in control trials for patients at all recording sites and for nonpatients at Fz and Pz. This reduction of CNV by letters is relatively greater for patients than nonpatients at both Fz and Cz (see Fig. 1). For the psychosurgery patients then, CNV development appeared to be more disrupted by a short-term memory task than for nonpatient controls.

As shown in Table 1 and Fig. 1b, there is a pattern of elevation of CNV amplitude in no-letter trials compared to control trials for nonpatients ($p < .02$ for Cz; $p < .10$ for Pz) but not for patients, who show a pattern of slight CNV decrease in no-letter trials. Group differences between patients and nonpatients, shown in Fig. 1 for no-letter minus control difference scores, are significant for Cz and approach significance for Fz ($p < .10$). Thus, the pattern of a rebound in CNV amplitude seen on no-letter trials for nonpatients is missing in patients.

In conclusion, patients receiving psychosurgery show greater disruption in CNV development defined in two ways—greater amplitude reduction by a short-term memory task for letters and a lack of recovery from this disruption as shown by absence of a CNV rebound function. The fact that the patients are older than nonpatients raises the question of possible organic deterioration due to the normal aging process rather than surgery. Preliminary findings indicate that elderly individuals show a clear lack of CNV rebound only at Fz. Since departures from normal CNV reported for psychosurgery patients appeared at other than the Fz location, whatever organic factors contributed to CNV impairment are likely to be outside the normal aging process. In addition, it is unlikely that surgery alone (intended for frontal brain areas) could account for the absence of CNV rebound in the posterior (Pz) recording site. Aside from the lesions in the frontal white matter, other factors that differentiate the two groups include psychopathology, previous history of medication, and/or electroshock therapy. Baseline CNV amplitude values were comparable for patient and nonpatient groups; rebound values were not. The possibility of the influence of these other variables that distinguish the two groups cannot be ruled out. Whatever the underlying neurophysiological mechanisms responsible for these changes, the CNV rebound effect appears to reflect a type of brain function not detectable in the routine measurement of baseline CNV (in control trials).

Acknowledgments

The assistance of Debra Yrchik and Debbie Meinbresse in carrying out the study and Tim Clifford and Connie Dessonville in data analysis is gratefully acknowledged.

Table 1. Means (and Standard Deviations) for Amplitude of Contingent Negative Variation [a]

		CNV amplitude, (μV)		
		Fz	Cz	Pz
Nonpatients (n = 14)	Control	5.18 (5.86)	11.41 (7.32)	8.37 (5.97)
	Letters	1.15[b] (3.93)	9.68 (4.73)	3.50[b] (5.17)
	No letters	8.83 (7.24)	16.23[b] (7.47)	12.62 (6.06)
Patients (n = 19)	Control	6.75 (6.97)	13.54 (10.18)	9.72 (7.00)
	Letters	-3.06[b] (6.07)	3.49[b] (9.63)	3.26[b] (10.11)
	No letters	5.53 (7.11)	10.86 (12.13)	9.52 (9.53)

[a] For simplicity, CNV negativity is presented as algebraically positive.

[b] Significantly different from control ($p < .05$).

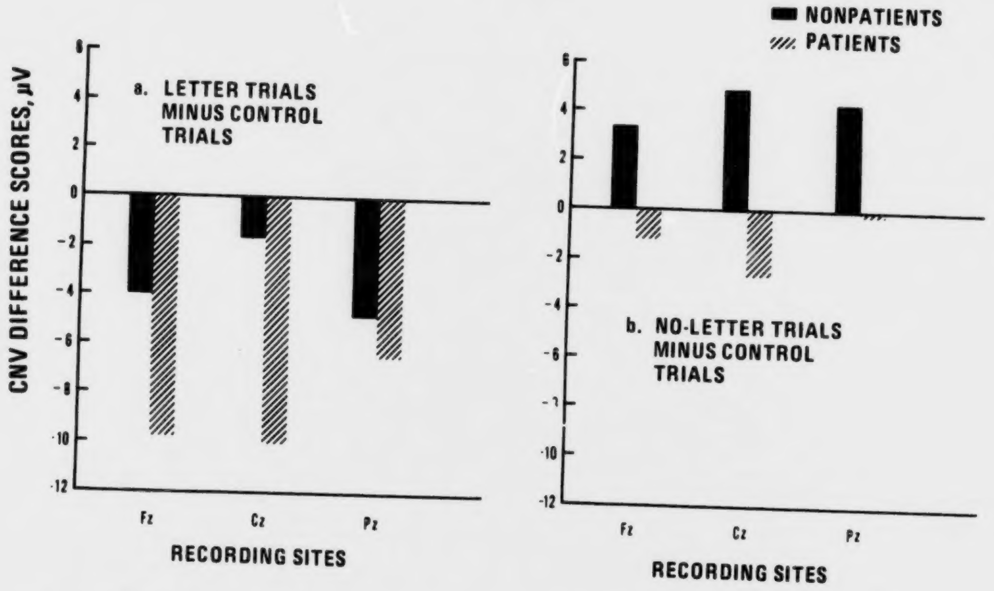

Fig. 1. CNV amplitude difference scores in psychosurgery patients (n=19) and nonpatient controls (n=14). The downward direction of bars in a indicates reduction in CNV amplitude in letter trials relative to control trials. The upward direction of bars in b indicates enhancement in CNV amplitude in no-letter trials relative to control trials, while the downward direction indicates reduction in CNV amplitude in no-letter trials relative to control trials.

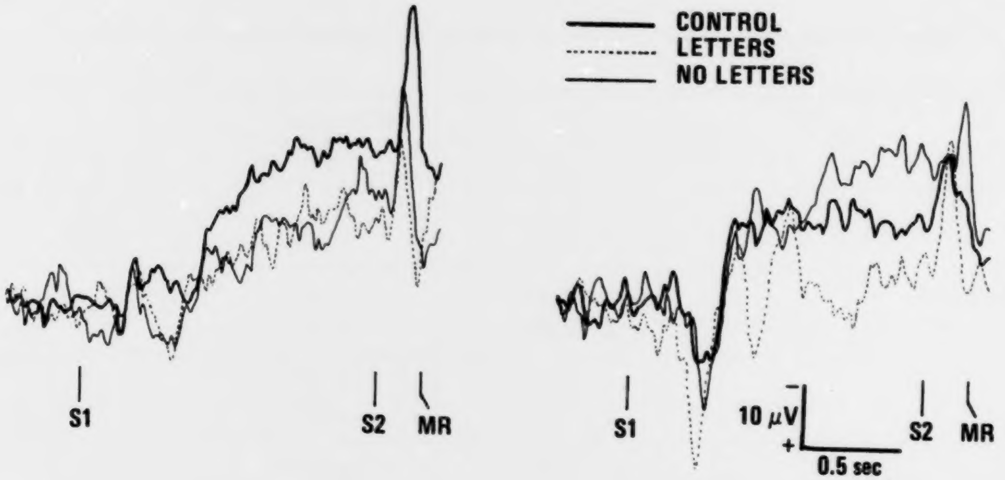

Fig. 2. Examples of vertex (Cz) CNV traces of a psychosurgery patient (left side of figure) and a normal volunteer subject (right side of figure) for control, letter, and no-letter trials. For the normal subject, there is an elevation in CNV magnitude for no-letter trials compared to control trials (CNV rebound effect) that is missing in the psychosurgery patient. Negativity at the Cz recording site relative to linked earlobes is shown as upward.

SOME METHODOLOGICAL AND THEORETICAL ISSUES OF ERP IN PSYCHIATRIC POPULATIONS

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Results obtained by recording event-related slow potentials (ERP) from psychiatric patients in Liege and Montreal have been reported in the proceedings of the three previous ERP meetings (Dongier et al. 1973, Dubrovsky and Dongier 1976, Timsit-Berthier et al. 1969). Since these findings have not been replicated in other laboratories, we think it important to comment on certain methodological aspects that may account in part at least, for some of the discrepancies. We should also like to raise some issues pertaining to the interpretation of ERPs in psychiatry.

ERP recording techniques have not yet been standardized. Serious limitations in interpretation are posed by the use of techniques that cancel out from scalp-recorded activity potentials originating in extracerebral sources. Such is the case when potentials originating during eye movements recorded bipolarly (Hillyard and Galambos 1970, McCallum and Walter 1968) are substracted from brain potentials recorded monopolarly as conventionally done for CNV and readiness potential (RP). As noted by Cooper (1959) bipolar derivations can seriously exaggerate the phase and time difference in records of activity from sources that are not radial, symmetrical, and stationary. Substracting bipolarly derived EOG potentials from conventionally recorded CNV and RP is then a very hazardous procedure.

Furthermore, since cerebral potentials can reach the electrodes for eye-movement recording (EOG), they may be cancelled out when potentials derived from the EOG are subtracted from potentials recorded from the vertex (Papakostopoulos et al. 1973; Rosen, this volume). It is possible then, that cancellation of vertex-derived brain potentials by anomalous compensation from EOG potentials recorded in parallel may eliminate significant phenomena of cerebral origin.

In our laboratories, we monitor the influence of eye movements on event-related brain potentials by recording in a parallel channel from a supraorbital electrode referred to the linked earlobes electrode. We use the same reference to record CNV and RP. The amplification and time constant (9.5 sec) is also similar for both the vertex and supraorbital channels (Dubrovsky et al. 1973).

Another aspect that deserves serious consideration, especially in psychiatric populations, is the instructional set given to the subjects. A graphic example of the importance of prior instructions and their influence on ERP characteristics is shown in Fig. 1. The CNV recorded from subjects suffering from specific phobias is significantly larger and more prolonged when phobogenic stimuli are used as S2 (Fig. 1B) (Barbas et al., this section), than when non-disturbing stimuli are used (Fig. 1A). In Fig. 1C, the patient was expecting the phobogenic stimuli because of misinterpreted instructions. Consequently, even though non-disturbing stimuli were actually used as S2, the CNV obtained had characteristics like the ones obtained when phobogenic stimuli were employed (Fig. 1B). This result indicates that the expectation of phobogenic stimuli has greater influence in determing the CNV amplitude and duration than the characteristics of the stimuli used *per se.*

The parameters generally evaluated in ERP (amplitude and duration) presuppose that the central nervous system (CNS) is an energy transfer system. We are searching, with the help of sophisticated computer analyses, for changes in overall levels of electrical activity that either accompany, or cause, mental disease. We are still working within the framework of the Freudian dictum of looking at changes in quantities of energy (physical or chemical) to account for psychopathological changes in behavior. It appears to us that a method for analysing ERP that allows searching for qualitative changes in brain waves and for predominance of certain cerebral areas at different stages, rather than for an evaluation of overall level of activity, will be more in accordance with the present-day views that consider the nervous system as an information transfer system (Dubrovsky and Melzack 1970, Dubrovsky and Dongier 1976).

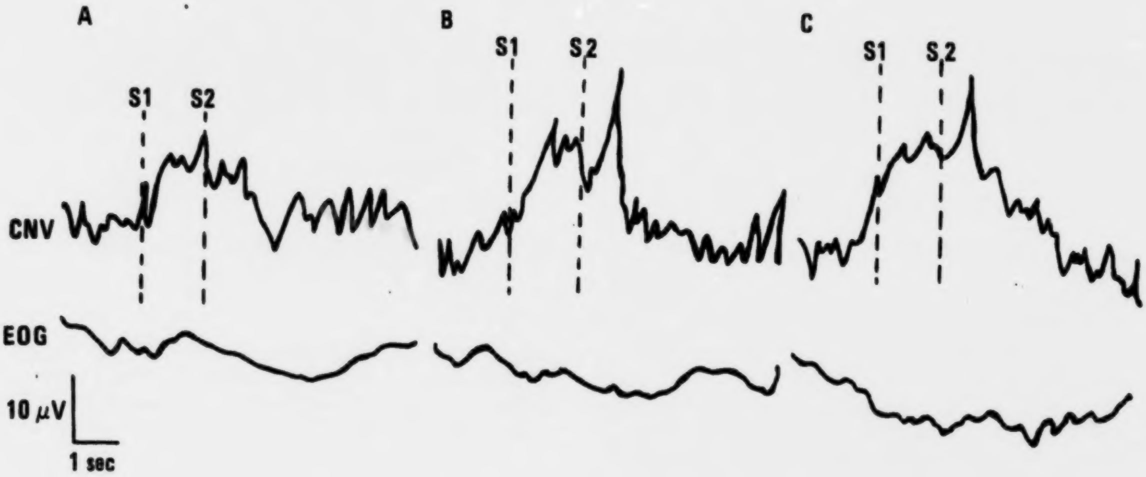

Fig. 1. Contingent negative variation and eye movement potentials for patient suffering from phobia to snakes: A. when presented in S2 with a picture of a cat (nondisturbing stimulus), B. when presented in S2 with a picture of a snake (phobogenic stimulus), and C. when presented in S2 with a picture of a cat, but was expecting the picture of a snake because of misinterpretation of instructions.

Trends in this direction include the analysis of CNV form under different behavioral requirements during recording (Weinberg et al. 1976). In addition, studies of the topographical distribution of ERPs have revealed significant differences in CNV form, recorded from different leads in normal subjects (Weinberg and Papakostopoulos 1975). At EPIC IV, Tecce also reported that abnormally prolonged postimperative negative variation (PINV) (Dongier 1973a) during a standard CNV paradigm can be observed in psychiatric patients only from certain leads.

These observations reopen the issue of the possible differential origin of the prolonged PINV, which may be cortical (Dubrovsky et al. 1976), as opposed to the CNV wave *per se*, which appears to be triggered subcortically (Gazzaniga and Hillyard 1972, McCallum et al. 1973). Work using prolonged reaction time foreperiods (4 sec or more), during the classical CNV paradigm (Loveless and Sanford 1975, Rohrbaugh et al. 1976, Weerts and Lang 1973), clearly reveals that different processes are involved in the generation and resolution of CNV phenomenon. These studies have serious implications for the interpretation of ERPs in psychiatry. In recent studies on electrophysiological manifestations of psychopathology (Shagass 1975, Callaway 1975), it has been emphasized that consistent alterations in later evoked activity recorded from frontal, nonprimary receiving areas, reflect alterations of the early evoked response. In these studies, it is assumed that late evoked activity in frontal areas is elicited from projections originating in primary sensory cortex, after being partly processed there. This assumption involves essentially a sequential type of sensory information processing.

As the bioelectrical activity that gives rise to CNV and RP is preferentially recorded from frontal brain areas, it is important to remember that evoked electrical activity in these areas can be elicited by activation of parallel fiber systems, independent of projections to primary receiving areas. Moreover, we have argued (Dubrovsky and Garcia-Rill 1971) that these parallel projection systems are involved with the processing of different aspects of the original input from the primary projection systems. The existence of parallel information processing in the CNS must then be taken into account when interpreting late frontal evoked responses. On account of the classical derivations for ERP, it will be of great importance to elucidate the question of whether the frontal brain potentials are mainly dependent on previously processed cortical neural activity or are independently generated from subcortical areas that do not project to primary sensory cortex (and are, therefore, part of a parallel system for information processing).

While we believe that the problems raised for discussion concern the general field of event-related slow potentials and behavior, we think that resolution of these problems is of utmost importance for a better definition and agreement of the uses (and abuses) of event-related slow potentials in psychiatry.

MORPHOLOGICAL ANALYSES OF THE CNV IN PSYCHIATRY: COMPARISON OF RESOLUTION MODE AND CUMULATIVE CURVE METHODS[1]

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Several years ago, with a purely empirical and medical point of view, a morphological classification system based on the "resolution mode" of the CNV was developed at Liege (Timsit-Berthier et al. 1973). Although this technique was of some value in distinguishing slow potential patterns of mental patients from those of control subjects, morphological analysis provided little help in the differential diagnosis of psychotic and neurotic patients. In order to improve the diagnostic sensitivity of the electrophysiological test, the recording session was extended and a cumulative method of assessing the temporal evolution of SPs was developed. In this report, the cumulative curve method will be described and compared with the earlier resolution mode method.

Method

Subjects

This study included 55 control subjects (17 men; 38 women; mean age, 29 years; S.D.=5.5) and 240 patients (166 men; 74 women; mean age, 33 years; S.D.=6.1). Ninety-four were recruited from the polyclinic of our department, 90 from the open psychiatric service of the general hospital, and 56 from the closed psychiatric service. The patient group included 85 psychotics and 75 neurotics. Eighty patients were rejected because of inadequate clinical data.

Apparatus

EEG was recorded at Cz with Ag/AgCl electrodes referred to linked earlobes using amplifiers modified to yield an 11-sec time constant with an upper cutoff of 50 Hz. EEG and EOG were recorded on FM tape for off-line summation. Five to 35 percent of the trials from individual subjects were rejected because of EOG deviations, muscular artefacts, or erroneous responses.

Experimental procedure

The recording room was darkened and isolated from outside sounds by white noise delivered over loudspeakers at low intensity. Subjects were asked to keep their eyes closed during testing. In a 1-hour session, subjects received a block of 100 stimuli pairs. Each trial began with a warning click (S1) followed after 1.5 sec by a series of clicks (S2), which the subject terminated by pushing a button with the right hand. The interval between the motor response and the warning stimulus for the next trial varied randomly from 10 to 30 sec. Six to 8 successive averages (12 trials each) were calculated for each block of 100 trials.

Resolution mode analysis

The first 12 trials were averaged and analyzed for resolution mode. Baseline was estimated visually as the average voltage of the 1000-msec pre-S1 epoch. CNV amplitude was measured as the average voltage of the 200-msec pre-S2 epoch relative to baseline. The resolution mode of the CNV for each subject was also judged as described in the paper by Timsit-Berthier et al. (this section).

When CNV amplitude and resolution mode had been determined, all waveforms were classified according to statistical data as "normal" or "abnormal" as illustrated in Fig. 1. "Normal" curves included Types I and II, while "abnormal" curves included Types III and IV as well as flat CNVs (amplitude $< 5 \mu V$).

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[1] Work was supported in part by grant 20397 - FRSM.

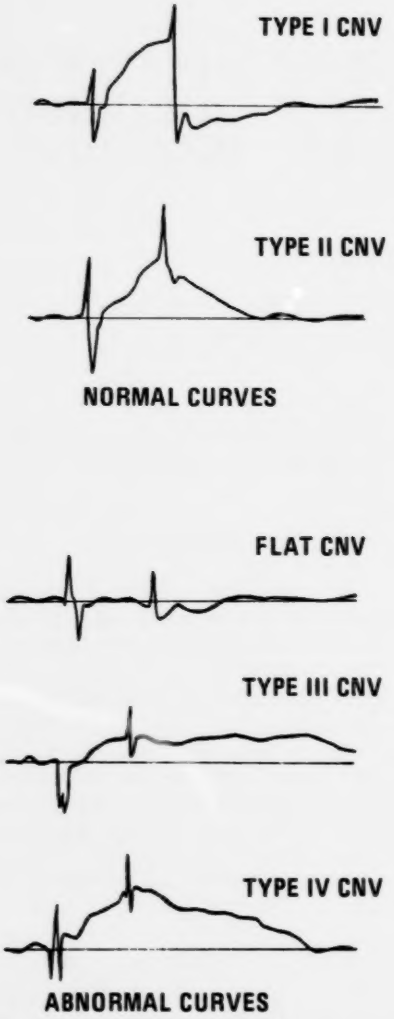

Fig. 1 Normal and abnormal curves classified on the basis of the resolution mode

Cumulative curve analysis

A method of cumulative analysis, illustrated in Fig. 2, was devised to reduce the amount of data obtained from the six to eight sequential averages obtained from each subject to a single positivity/negativity (O'P/ON) ratio. First, negative and positive measures were obtained for each sequential average. Negative values (CNV) were obtained as described above. Positive values were calculated as the mean voltage during a 300- to 500-msec post-S2 interval relative to the CNV value. Positive ($O'P=P_1+P_2+...+P_n$) and negative ($ON=N_1+N_2+...+N_n$) values of each average in the sequence were then summed, and the cumulative values were expressed as the O'P/ON ratio. Cumulative curves of the positive and negative measurements were also drawn to illustrate graphically the temporal evolution of the phenomena (see Fig. 1B).

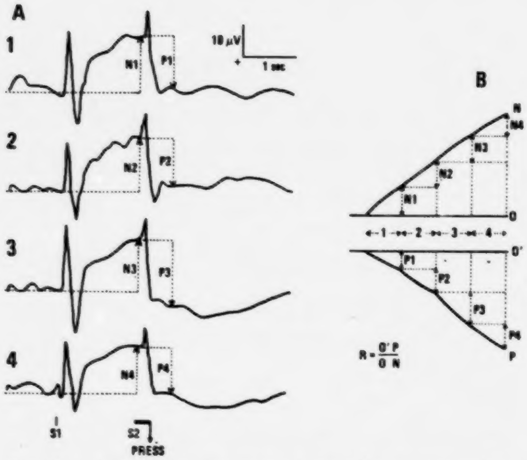

Fig. 2. Cumulative curve analysis of slow potentials. A. Principle of measurement: measures of pre-S2 negativity (n) and post-S2 positivity (p) are obtained for sequential series of 12 trials. B. Cumulative display and reduction of data: cumulative curves are constructed for successive positive and negative values. The cumulative sum of positive (O'P) and negative (ON) values are then expressed as the cumulative ratio (R).

According to statistical data, cumulative curves were then classified as "normal" or "abnormal" as shown in Fig. 3. In brief, normal cumulative curves included: (1) Type I or II patterns with relatively

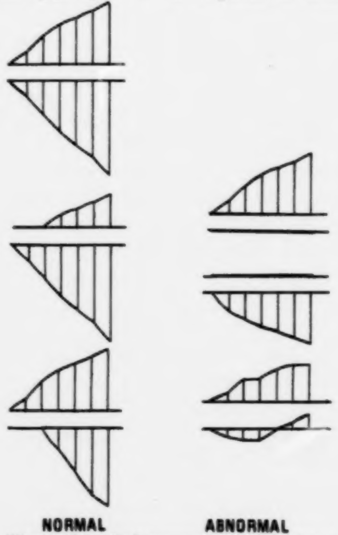

Fig. 3. Normal and abnormal cumulative curves classified on the basis of the six successive measures of pre-S2 negativity and post-S2 positivity.

invariant positive and negative amplitudes across time (2) initially flat CNVs, which progressively increased in negativity across time; and (3) initially prolonged Type III or IV CVNs, which progressively decreased in duration across time. Abnormal cumulative curves included: (1) Type III, IV, or flat CNVs, which remained relatively invarient across time, or (2) a labile temporal pattern of CNVs (e.g., flat, then Type III, then Type I) with O'P/ON<-0.1.

Results and discussion

Results of the resolution mode and cumulative curve analyses are shown in Fig. 4 and 5, respectively. Note that the cumulative curve method classified practically all normal control and neurotic subject SP patterns as "normal," but classified psychotic patient SPs as "abnormal" 49% of the time. The discriminant power within the psychotic population, therefore, was greater for the earlier resolution mode than the cumulative curve method. Neither method, in fact, provides an unequivocal measure for the differential diagnosis of neurotic versus psychotic syndromes.

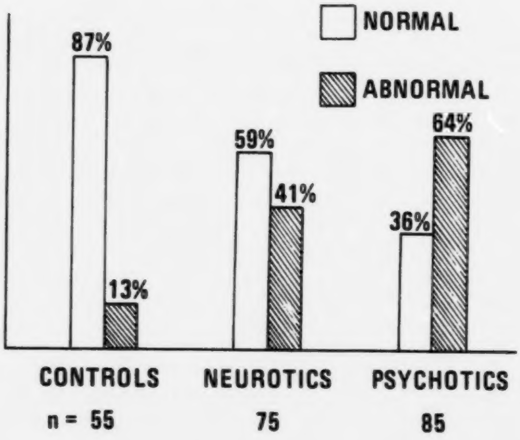

Fig. 4. Results of the resolution mode classification of slow potential patterns observed in control, neurotic, and psychotic subjects.

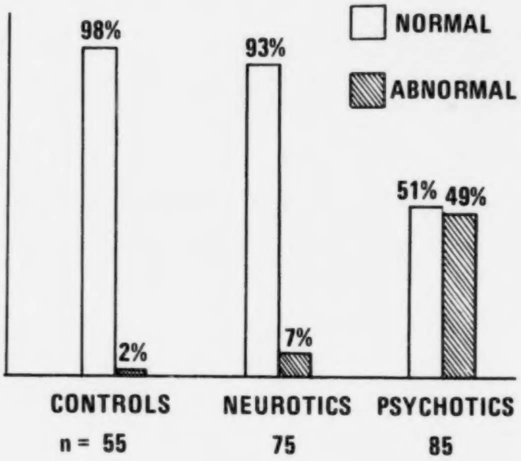

Fig. 5. Results of the cumulative curve classification of slow potential patterns observed in control, neurotic, and psychotic subjects.

However, results of this comparative evaluation do provide some optimistic signs. While a normal cumulative curve for a psychotic subject has no particular meaning and does not in the least preclude a diagnosis of psychosis, an abnormal cumulative curve (O'P/)N) ratio -01) allows us to affirm a diagnosis of psychosis within a very small margin of error. It is also apparent that the temporal analysis of evolving slow potential patterns provides a different, and probably more sensitive, index of mental state than a single CNV provides. It is worthwhile to point out that the cumulative curve method also includes a second phenomenon (usually called the P300 wave) in the diagnostic equation. Further refinement of the electrophysiological criteria for differential diagnosis is obviously needed. On the other hand, morphological analysis of slow potentials has provided to be a useful adjunct to traditional diagnostic procedures at Liege for many years (Timsit-Berthier et al. 1970, 1973, 1975).

SOMATOSENSORY EVOKED POTENTIAL AS A MEASURE OF TOLERANCE TO ETHANOL[1]

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Ethanol, in amounts commonly imbibed at social functions, reduces the amplitude of late components of evoked potentials recorded from central scalp regions. Gross et al. (1966) reported that 100 cm^3 of 90-proof whiskey substantially reduced the amplitude of components of the auditory evoked potential between 30 and 220 msec, recorded from a left central scalp region. Lewis et al. (1970) found a similar influence of ethanol on components from approximately 130 to 230 msec of the visual and somatosensory evoked potentials at blood alcohol concentrations (BACs) ranging from 70 to 100 mg%. Significant changes occurred at C3 and C4, but not at 01 and 02. Salamy and Williams (1973) confirmed the effect of ethanol on the somatosensory evoked potential (SEP) at the vertex and provided evidence that amplitude reduction was not the result of gross changes in background EEG or of increases in variability of peak latency. They showed also that speed of peripheral nerve conduction was unchanged and that short-latency components of the SEP resulting from specific nervous input were resistant to the presence of ethanol, except at high concentrations (145 mg%). The observation that ethanol-induced decrement of evoked potential amplitude occurs primarily in late components often associated with cognitive functions suggested that the amount of evoked potential decrement might relate to drinking history, since experienced drinkers evidence less cognitive disruption from a given amount of ethanol than do inexperienced drinkers. Objectives of the present work were to replicate the effect of ethanol on the vertex-recorded SEP and to determine the relation between SEP change and drinking history.

Methods

Eleven males were chosen on the basis of a drinking history questionnaire, modified from that of Cahalan and Cisin (1968). The subjects ranged in drinking history from one or two beers a month to two cocktails or five beers nearly every day, plus moderate intake of other alcoholic beverages.

Subjects were studied during 2 nonconsecutive days. The placebo day was first. Three drinks were served, each of 200 ml orange juice with a sufficient quantity of 95% USP ethanol floated on top (2 ml per drink) to resemble the odor of an actual mixed drink. On the second day, subjects received 0.9 g/kg ethanol in three equal drinks of 200 ml of orange juice. Each drink was imbibed over a period of 10 min.

Fig. 1 illustrates the daily schedule. Subjects had fasted for at least 4 hours before the start of the experiment, usually since the preceding evening meal. They were given a light breakfast (toast) before recording and stimulating electrodes were applied. Testing began at 0930 and continued in 0.5-hour sessions. Drinks were given from 1030-1100, lunch was from 1230-1300, and a relaxation period was held from 1430-1500. Data from individual testing sessions were grouped in the predrink, midday, and late afternoon time periods (see Fig. 1). Because of rapid changes in BAC, data from only the 1130-1200 testing session of the morning period were used.

Ag/AgCl cup electrodes were applied at vertex and mastoids. EEG was amplified and recorded (bandpass 0.02-30.0 Hz, 8-sec TC). Beckman Biominiature electrodes were attached superior and lateral to one eye. SEPs were elicited by 500-μsec pulses delivered through a stimulus isolation unit with a predetermined pseudorandom sequence of interstimulus intervals ranging from 2-6 sec in 0.5-sec increments. The cathode was a flat Ag disk, applied over the median nerve 2 cm proximal to the flexion crease of the wrist. The anode was a large metal plate on the dorsal surface of

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[1] This research was supported, in part, by Department of the Navy, Bureau of Medicine and Surgery, under Work Unit MR000.01.01-6006. The views presented in this paper are those of the authors. No endorsement by the Department of the Navy has been given or should be inferred.

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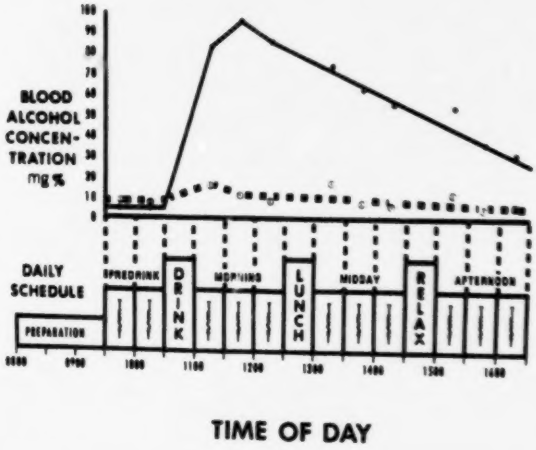

Fig 1. Lower portion: Daily time schedule for both placebo and drug days. Upper portion: Average blood alcohol concentrations for 11 subjects plotted in time relationship to daily schedule (drug day: solid line).

the wrist. Subject ground was placed on the upper portion of the stimulated arm. Current was set near 1 mA to produce a minimally observable thumb twitch. Care was taken to maintain a constant effective current by continually monitoring the extent of the thumb twitch and by measuring impedance before each series of stimulations, adjusting voltage appropriately. Sixty to 72 electrical stimulations were given in a recording session. Subjects were instructed to count the number of stimulations to themselves, to visually fixate a spot on the wall, and to refrain from blinking in the 1 sec following an electrical stimulation. Breathalyzer readings (Smith and Wesson Model 1000) were taken at the midpoint of each 0.5-hour session, following SEP recording. Behavioral tests and a mood scale were administered, but these are not discussed in this report.

Evoked potentials were averaged off-line on a PDP-12 computer. Trials associated with eye or movement artifact or with EEG signs of drowsiness were excluded. An average consisted of the first 32 acceptable trials in any one recording session. All statistical comparisons were two-tailed and were evaluated at the 0.05 level. Dunn-Bonferroni criteria (Dunn 1959) are indicated in tables.

Results

BAC values

Average BAC values for the 11 subjects are plotted in the upper portion of Fig. 1. On the placebo day (dashed line), BAC remained at or below the 10 mg% noise level of the Breathalyzer, except in the morning period when the 6 ml of ethanol used in the placebo drinks produced a slight increase in BAC. On the drug day (solid line), BAC rose rapidly, to peak at about 1145, and then fell slowly. One subject achieved peak BAC at 1115, three at 1215, and one at 1315. Peak BACs ranged from 77-121 mg% (mean 94).

SEP waveform

Fig. 2 illustrates the components of averaged SEPs, a positivity at 100 msec (P1), a negativity at 155 msec (N1), and a broadly peaked positivity from 220-400 msec (P2). The latter peak sometimes consisted of two positive peaks at 230 and 300 msec, although not consistently enough to allow analysis as separate peaks. No components were detected consistently prior to about 70 msec, and there was no late negativity at about 350 msec as reported by Salamy and Williams (1973) and by Lewis et al. (1970). Peak-to-peak measures of amplitude were used: P1N1 and N1P2. Predrink SEP amplitudes were stable for each subject. Accordingly, SEP amplitudes did not differ significantly from one predrink testing session (0930-1000) to the next (1000-1030) or from the placebo to the drug day. Predrink SEP amplitudes, however, were variable among subjects. P1N1 ranged from 6 to 46 μV (mean 19); N1P2 ranged from 14 to 71 μV (mean 35).

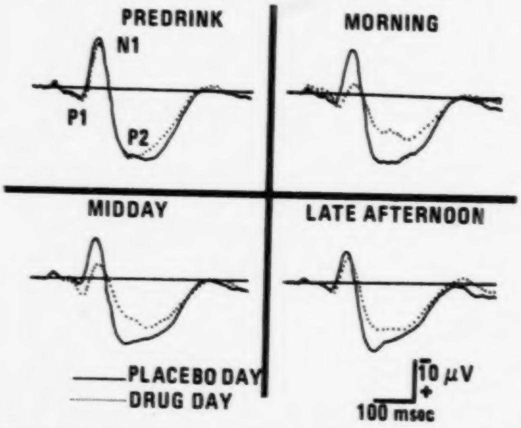

Fig. 2. Composite averaged somatosensory evoked potentials for 11 subjects during four time periods: predrink (704 trials), morning (352 trials), midday (1056 trials), and late afternoon (1056 trials). Epoch length was 500 msec. Stimulus was at trace onset. Reference level drawn was through averaged EEG 50-msec poststimulus.

Alcohol and evoked potential amplitude

Alcohol clearly reduced the amplitude of the vertex-recorded potentials (Table 1). Fluctuations are expressed in Table 1 in terms of percentage change from predrink amplitude, usually percentage decrement. On the placebo day, both peak-to-peak measures

Table 1. Percentage Decrements from Predrink Period of SEP Amplitude on the Placebo (P) and Drug (D) Days

	P1N1			N1P2		
	Morning	Midday	Late afternoon	Morning	Midday	Late afternoon
(P) Mean	5	14	25	5	11	22
(P) S.D.	26	22	18	10	19	18
(P) t-test	1.638	2.111	4.606	1.658	1.920	4.054
(P) Sig.[a]	(ns)	(ns)	<0.001	(ns)	(ns)	<0.01
(D) Mean	36	18	10	40	24	4
(D) S.D.	42	37	32	19	27	29
(D) t-test	2.843	1.614	1.036	6.982	2.948	0.458
(D) Sig.[a]	<0.02	(ns)	(ns)	<0.001	<0.02	(ns)

[a] For difference from population mean of zero; df=10, two-tailed. Dunn-Bonferrono criterion: 0.05/12=0.004

showed a gradual decline in amplitude (an increase in percentage decrement) from the morning to the midday period. This decline was significant by late afternoon. Percentage decrements on the drug day were corrected for the gradual decline in amplitude observed on the placebo day by subtracting the placebo day percentage changes from those observed on the drug day. This correction assumed that habituation and time-of-day effects on SEP amplitude were constant on both days. Drug-day percentage decrements were greatest in the morning period, declining in later periods. Fig. 2 illustrates (1) the similarity of predrink potentials on both days, (2) the gradual decline in the amplitude of placebo-day potentials, and (3) the marked decline in amplitude in the morning period of the drug day. Note that, without the placebo-day potential for comparison in the late afternoon, it would be difficult to determine the extent of the amplitude reduction resulting from ethanol.

Drinking history and amount of change in evoked potential amplitude

The five subjects ranked lightest in drinking history will be referred to as "light" drinkers; the six ranked heaviest, as "heavy" drinkers.

Two relationships were evident between drinking history and percentage decrement of evoked potential amplitude. On the drug day (Table 2, bottom half), light drinkers showed significantly larger percentage decrements in P1N1 amplitude in the morning and midday periods than did heavy drinkers. Further, there was a significant correlation of drinking history with decrement in the P1N1 measure in the morning and midday periods. Larger percentage decrements were associated with lighter drinking history. Correlations of N1P2 with drinking history showed a nonsignificant trend in the same direction. Light and heavy drinker groups did not differ significantly in weight, age, mean predrink SEP amplitude, or BAC characteristics, including ascending and descending slope, peak, time to peak, or mean predrink value (Table 3).

The second relation between drinking history and decrement in evoked potential amplitude occurred on the placebo day (Table 2, top half). Percentage decrement of N1P2 correlated significantly with drinking history during the morning period, with greater percentage decrements associated with heavier drinking history, the opposite of the observed effect as a result of ethanol on the drug day. Mean predrink SEP and BAC values did not vary significantly with drinking history on the placebo day (Table 3), except for a significant correlation between drinking history and mean predrink BAC.

Discussion

These data replicate the finding of Salamy and Williams (1973) that ethanol reduces the amplitude of the vertex-recorded SEP. The data also indicate that the amount of amplitude reduction is related to the amount an individual drinks and the frequency with which he drinks. Two unexpected observations were that long-term habituation of SEP amplitude occurred over the course of 7 hours and that rate of habituation without alcoholization may itself be related to drinking history.

While showing a reduction in amplitude resulting from ethanol, the present study did not show a clear-cut inverse relation between BAC and evoked potential amplitude as reported by Salamy and Williams (1973). Maximal decrease in evoked potential amplitude occurred with peak BAC for only 3 of 11 subjects. Equal

Table 2. Drinking History and SEP Amplitude: Percentage Decrements from Predrink Period on the Placebo (P) and Drug (D) Days

	P1N1			N1P2		
	Morning	Midday	Late afternoon	Morning	Midday	Late afternoon
Mean (P) of light drinkers	9[a]	8	17	2[a]	6	14
S.D.	28	30	18	8	26	22
Mean (P) of heavy drinkers	17	20	31	11	15	28
S.D.	18	14	16	8	13	11
U	6	14	9	4.5	13.5	10.5
Sig.	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)
rho	-0.450	-0.155	-0.296	-0.770	-0.232	-0.465
Associated _t_-value	-1.512	-0.471	-0.930	-3.620	-0.716	-1.576
Sig.	(ns)	(ns)	(ns)	< 0.01	(ns)	(ns)
Mean (D) of light drinkers	67	44	27	49	39	16
S.D.	9	15	8	20	21	23
Mean (D) of heavy drinkers	9	3[a]	4[a]	32	12	6[a]
S.D.	41	36	39	14	26	31
U	0	3	6.5	8	7	7
Sig.	0.004	0.03	(ns)	(ns)	(ns)	(ns)
rho	0.791	0.655	0.446	0.536	0.582	0.527
Associated _t_-value	3.879	2.600	1.495	1.905	2.147	1.860
Sig.	<0.01	<0.05	(ns)	(ns)	(ns)	(ns)

[a] Percentage increment in amplitude from predrink period. Dunn-Bonferroni criterion: 0.05/24= 0.002.

decreases in amplitude at equivalent ascending and descending BACs occurred in only 4 of 20 instances. Habituation (average 5% by 1130-1200) is not a likely source for the discrepancy between the two studies. Breathalyzer readings may not have been frequent enough in either study for accurate determination of time and value of peak BAC. Whatever the cause, the discrepancy is important as it relates to the nature of the effect of ethanol on evoked potential amplitude. Jones and Vega (1972) and Jones (1973) report that certain aspects of cognitive functioning are most disrupted during ascending BAC. If ethanol-induced amplitude reduction is related to the degree of disruption of cognitive ability, should not maximal decrease in evoked potentials occur during ascending BAC? The question is unanswerable from the present data and from those of Salamy and Williams (1973) since subjects were required in both studies only to count the stimuli. Subjects in the present study counted accurately except when drowsy. Evoked potentials recorded during tasks sensitive to ethanol might relate more meaningfully to the data of Jones and Vega (1972) and Jones (1973).

SEPs of moderately heavy drinkers were affected less by the intake of ethanol than were those of individuals with much less drinking experience. The cause for this differential reduction is unknown, but is interpreted here as related to chronic tolerance to ethanol. Tolerance, in turn, is thought to be associated with the responsiveness of the nervous system to ethanol rather than to a change in the rate of ethanol metabolism (Kalant et al. 1971, Mendelson 1971). The latter was ruled out as a factor in this study (Table 3). A major implication of the present results is that a clinically useful range of tolerances exists even among light to moderately heavy drinkers. Therefore, measures such as the SEP may allow the characterization of changes

Table 3. Controlled Variables in Comparing Light and Heavy Drinkers

	Age, yr	Weight, kg	Mean predrink SEP amplitude, μV				Peak BAC,[a] mg%	Time to Peak BAC,[a] hr	BAC slope,[a] mg%/hr		Mean predrink BAC, mg%	
			Placebo		Drug							
			P1N1	N1P2	P1N1	N1P2			Ascending	Descending	Placebo	Drug
Mean of light drinkers	30	73	17	40	17	36	90	1.41	58.7	15.4	5	9
S.D.	3	8	8	13	7	8	18	0.28	58.0	3.7	3	9
Mean of heavy drinkers	33	82	21	35	19	30	96	1.52	61.5	16.0	8	5
S.D.	4	11	12	16	12	15	8	0.28	11.9	2.5	4	3
U.	6	8	9	10	15	9	7.5	11	12	15	7.5	11.5
Sig.	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)
rho	0.553	0.378	0.524	-0.182	0.223	-0.205	0.328	0.009	0.309	0.214	0.598	-0.475
Associated t-value	1.991	1.225	1.846	-0.555	0.686	-0.628	1.042	0.027	0.975	0.657	2.238	-1.619
Sig.	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	(ns)	0.05	(ns)

[a] Drug day. Dunn-Bonferrono criterion: 0.05/12=0.004.

in tolerance preceding alcholism, even though the biochemical bases of tolerance are still under investigation.

The correlation between drinking history and decrement in amplitude of N1P2 during the morning period of the placebo day is puzzling. The gradual amplitude decline noted for all subjects on the placebo day appears to be a long-term habituation. This interpretation is supported by the full recovery of amplitude in the predrink period of the drug day. Why would individuals with a history of moderately heavy drinking and, by inference, with a relatively high tolerance to ethanol, consistently show greater habituation than light drinkers to 11 repetitions of a short series of electrical stimulations? Predrink BACs are an unlikely factor since, on the average, they fell within the 10 mg% noise range of the Breathalyzer (Table 3). The 6 ml of ethanol in placebo drinks may have had an influence. The different rates of habituation may have occurred by chance. Or, it may be that habituation and tolerance have features in common and that rate of habituation can be used as a measure of tolerance without the administration of ethanol.

There are only a few objective measures of tolerance that can be obtained and quantified in a clinical setting (e.g., optokinetic nystagmus, Mizoi et al. 1969). As a result, the process of tolerance is poorly understood, and the relation of tolerance to addiction is unknown. Alcohol rehabilitation centers could use noninvasive, easily administered measures of tolerance to determine the amount of Librium or other drug necessary to sustain patients while at various stages of withdrawal (Schuckit 1975). Measures of tolerance could also be used on general medical and surgical wards to determine whether surgical candidates suspected of alcoholism are denying the ailment and, thereby, are placing themselves in danger of receiving an insufficient dose of anesthesia. SEP measures, in combination with other measures, might provide a useful clinical index of chronic tolerance to ethanol.

Summary

This study examined the relationship of somatosensory evoked potentials (SEP) and ethanol tolerance. Eleven male subjects were chosen on the basis of drinking histories ranging from light to moderately heavy. Vertex SEPs to median nerve stimulation were recorded on placebo and drug days. Ethanol (0.9 g/kg) was administered orally to obtain an average peak blood alcohol concentration of 94 mg% derived from Breathalyzer samples. The reduction in SEP amplitude during ethanol intoxication compared to placebo measures was inversely related to drinking habit (i.e., less reduction in heavy drinkers). Results suggest that the SEP may serve as a sensitive index of chronic tolerance to ethanol.

STIMULANT AND DEPRESSANT EFFECTS OF CIGARETTE SMOKING, NICOTINE, AND OTHER DRUGS ON THE CNV IN MAN[1]

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Although vast numbers of people smoke cigarettes, no one, including the smokers, seems to know why. Undoubtedly there is no simple explanation. Smokers often comment that they feel either 'relaxed' or 'stimulated' after a cigarette, although direct evidence of depressant or stimulant changes in the brain is difficult to obtain. An obvious way to study this problem is to examine the electroencephalographic changes that follow smoking. Murphree et al. (1967) and Lambiase and Serra (1957) found, in general, only stimulant effects. However, Armitage et al. (1969) reported both stimulant and depressant effects of cigarette smoke and nicotine in animals, both on electrocortical activity and on the release of acetylcholine from the cerebral cortex. The biphasic action of nicotine, i.e., its ability to first stimulate and then depress nervous tissue, has been known for a long time. This fact, coupled with statements of smokers concerning the stimulant and relaxant effects of nicotine and the findings of Armitage et al (1969) suggested that a biphasic action of nicotine in cigarette smoke ought to be detectable in the human brain. The contingent negative variation (CNV), first described by Walter et al. (1964), seemed to provide an appropriate measure, and the hypothesis was made that stimulant effects of nicotine on the brain might increase the magnitude of the CNV, whereas depressant effects might decrease it.

In order to study rigorously the action of nicotine in cigarette smoke, three series of CNV experiments were performed: (1) a study of the effects of cigarette smoking, (2) a study of the effects of drugs with known central stimulant and depressant actions, e.g., caffeine and nitrazepam, and (3) a study of the action of pure nicotine administered intravenously.

Cigarette smoking

Cigarette smoking was associated with significant changes in CNV magnitude which either increased or decreased after smoking (Ashton et al. 1973). Twenty-two regular smokers were studied and CNV increased in 7, decreased in 11, (and showed biphasic changes in 4, e.g. Fig. 1). If an increase or decrease in CNV magnitude reflects stimulant or depressant actions on brain activity, this study indicates that cigarette smoking can exert both effects in man. These findings are compatible with earlier studies on human performance in a car simulator which showed that reaction time could be either increased or decreased by smoking (Ashton et al. 1972a, 1972b). There was no correlation between the effects of cigarette smoking on the CNV and changes in heart rate, blood pressure, skin temperature, or blood carboxyhemoglobin. Moreover, sham smoking of an unlit cigarette had no effect on the CNV, suggesting that changes in CNV magnitude associated with smoking were in fact due to central actions of nicotine (Ashton et al. 1974).

From experimental work in animals, it is known that the effects of nicotine are dose-dependent, i.e., smaller doses cause central stimulation whereas larger doses cause depression. There is strong evidence that human smokers smoke for some optimum dose of nicotine by appropriate alterations in their smoking behaviour, particularly puffing rate (Ashton and Watson 1970). The dose of nicotine varies according to circumstances: a smaller dose was taken when subjects were carrying out a task, whereas larger amounts of nicotine were taken after the task. An important additional determinant of nicotine dosage is the personality of the smoker. Of 16 smokers,

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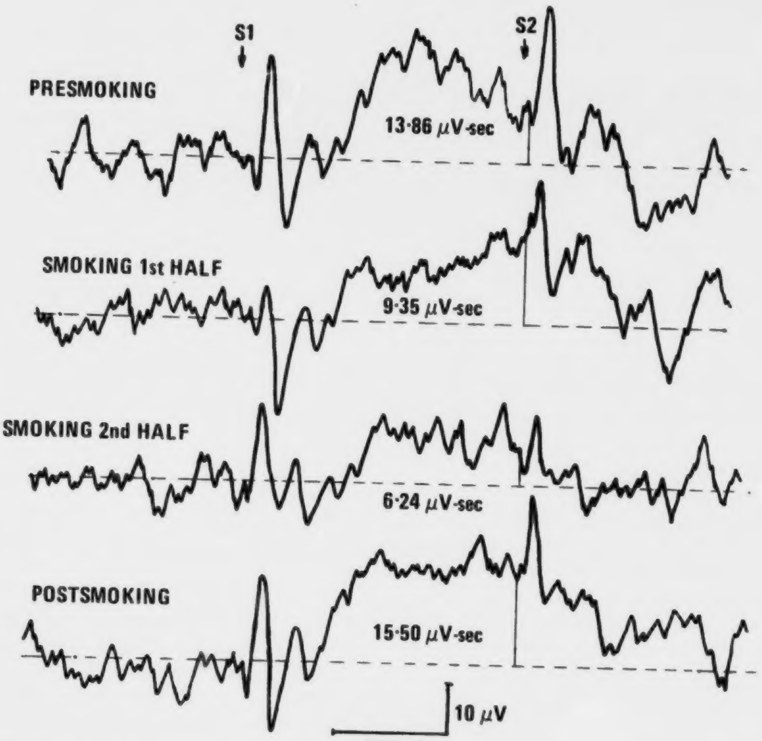

Fig. 1. CNVs (average of ten trials) in one subject showing decrease after smoking first and second half of one cigarette, with postsmoking recovery. CNV magnitude (μ V-sec) is indicated. S1 = flash (0.3 joules, 100 msec). S2 = tone (500 Hz). Calibration as shown. Negative up. (Reprinted from Ashton et al. 1978a by permission of the publisher.)

the 8 more extraverted subjects has a lower rate of nicotine intake, which produced a stimulant effect on the CNV, whereas the 8 more introverted subjects had a higher rate of nicotine intake, which depressed the CNV (Ashton et al. 1974). From these results, it was concluded that smokers unconsciously select different doses of nicotine from a cigarette in order to achieve some optimum dose that meets their own requirements, determined by circumstances and personality. As Armitage et al.(1968) stated, smokers have literal finger-tip control of nicotine intake.

Caffeine and nitrazepam

When it became evident that nicotine could either increase or decrease the magnitude of the CNV, it was considered essential to validate these results by examining the effects of known central stimulant and depressant drugs on the CNV. It has since been shown repeatedly that nitrazepam (2.5 mg) decreases and caffeine citrate (300 mg) increases CNV magnitude (Ashton et al. 1974).

These small doses, of nitrazepam and caffeine, although producing significant changes in CNV magnitude, did not cause significant alterations in heart rate or fingertip temperature and had virtually no subjective effects. It was concluded that the CNV was a sensitive and reliable indicator of drugs with central stimulant and depressant actions. Further experiments using other centrally acting drugs, such as pemoline and diazepam, have provided additional supporting evidence (Ashton et al. 1976 and unpublished results).

Pure nicotine administered intravenously

Having demonstrated that cigarette smoking produced both stimulant and depressant effects on brain activity in man, measured in terms of CNV effects, the next step was to determine whether the effects of cigarette smoking could be accounted for by the nicotine content of the smoke.

Armitage et al. (1969) had shown that intravenous (iv) nicotine in animals can mimic the effects of cigarette smoking if the drug is given as intermittent 'shots' but not if it is administered as a continuous infusion. Volunteers were therefore given intermittent iv injections of nicotine and physiological saline (as a control) using the technique described by Armitage et al. (1974). The dose of nicotine in each

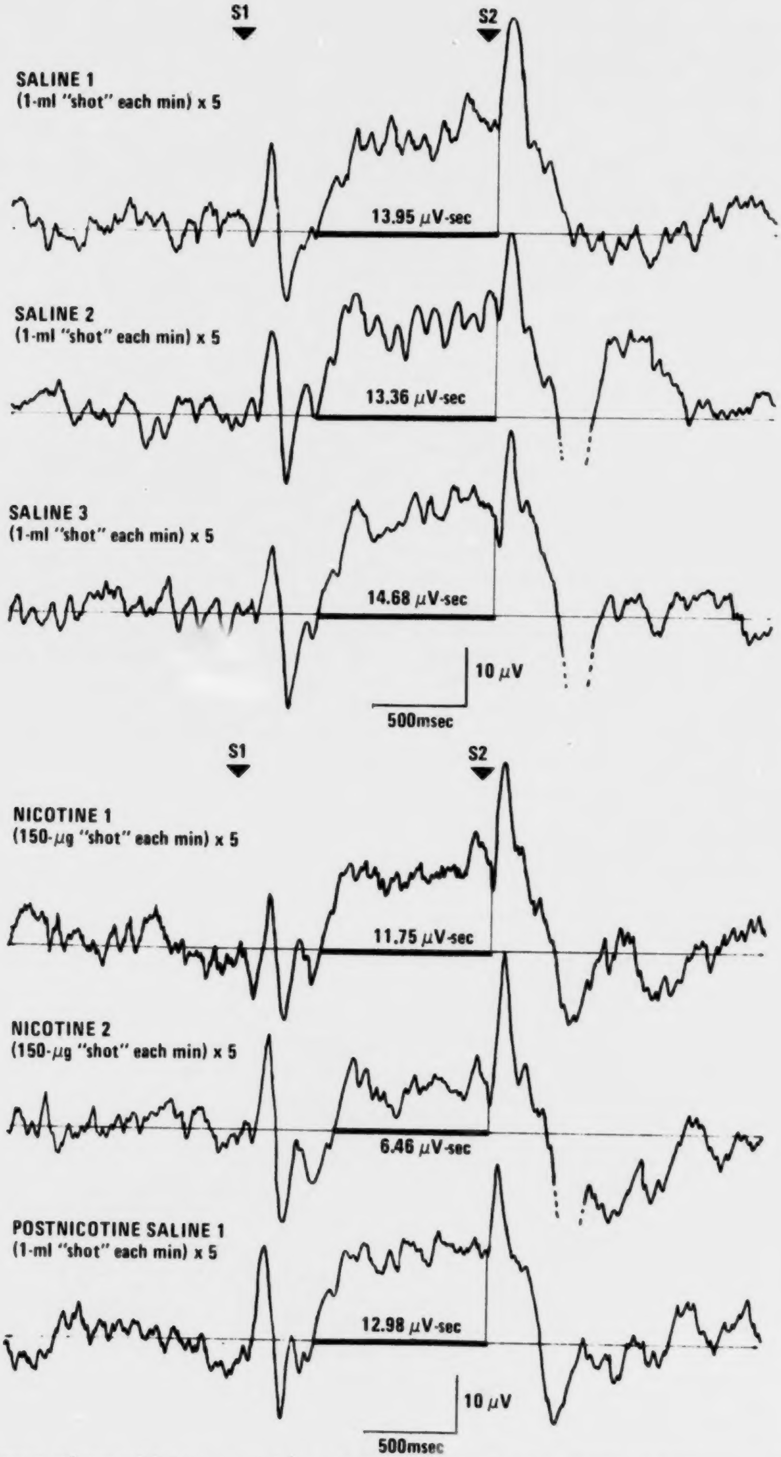

Fig. 2. CNV (average of ten trials) in one subject showing responses to six series of intravenous 'shots' (five per series) of physiological saline and nicotine (5 x 150 μ G = 750 μ g total). CNV magnitude (μ V-sec) is indicated. S1 and S2 as for Fig. 1. Negative up. (Reprinted from Ashton et al. 1978b by permission of the publisher.)

shot and the total amount of nicotine were comparable to that obtained by a cigarette smoker who inhales when smoking a cigarette of a brand with medium nicotine yield (1 to 2 mg) (Ashton et al. 1975, 1978).

After each series of shots of nicotine or physiological saline, the CNV was measured. Fig. 2 shows records obtained from one subject who received five shots of 150 μg nicotine on two occasions after control saline shots. There was a small reduction in CNV magnitude after the first dose of nicotine and a 50% reduction in CNV magnitude after the second dose. During the post-drug saline control, the CNV magnitude returned to normal.

During the initial experiments with intravenous nicotine, a single dose was administered to each subject based upon his smoking habits. Under these conditions, nicotine produced an increase in CNV magnitude in some subjects and a decrease in others. It then became important to determine whether the response of each subject depended on dose or whether it depended on the individual and was largely or completely independent of dose. Further experiments were carried out using a range of nicotine doses, and Fig. 3 shows the dose-response relationship in one subject; the relationship was characteristic for all subjects in the series. The dose-response curve is one of an unusual form in that the magnitude of the CNV at first increases with increasing doses of nicotine, but thereafter further increases led to increasing reductions in the magnitude of the CNV.

The results of the experiments using intravenous nicotine indicated that (1) the effects produced by cigarette smoking and pure nicotine are very similar and (2) nicotine is capable of causing a biphasic response that is dose-related. This biphasic effect of nicotine is not unique. For example, Tecce and Cole (1974) reported that 10 mg of amphetamine can produce behavioural alertness and increased CNV amplitude in some subjects, whereas in others it produces initial drowsiness and reduces the CNV

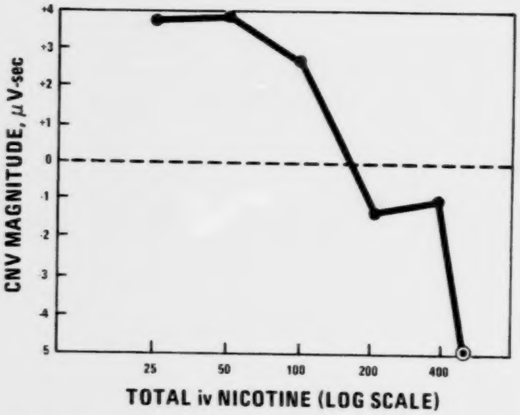

Fig. 3. Typical dose-response curve showing effect of intravenous nicotine (each dose given as five "shots"). Note: Highest dose given in separate experiment. (Reprinted from Ashton et al. 1978b by permission of the publisher.)

More recently, Pirch (this volume) has shown that amphetamine causes a biphasic dose-related effect on cortical slow potentials recorded from unanesthetised rats. All these findings, taken with the present results, emphacize the importance of dosage when studying the effects of drugs on event-related slow potentials.

Conclusions

In summary, it was concluded that changes in the magnitude of the CNV produced by cigarette smoking are principally due to nicotine absorbed from the inhaled smoke and that nicotine can exert either stimulant or depressant effects on the human brain. From the combined results of the series of experiments, it was also concluded that the CNV is a sensitive, reproducible, and quantitative test for the central effects of drugs; that it has been the means of throwing light on the effects of cigarette smoking on the human brain; and that it has given considerable insight into the reasons why people smoke.

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VII. ENVIRONMENTAL NEUROTOXICOLOGY

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NEUROBEHAVIORAL ASSESSMENT OF ENVIRONMENTAL INSULT

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An extensive correspondence among environmental toxicology panelists was undertaken prior to EPIC IV to identify critical issues for discussion. These questions are reviewed here[1] and elaborated in the papers that follow. The issues are primarily methodological ones dealing with the comparative sensitivity and utility of neurobehavioral measures in the assessment of environmental insult. The papers also report neurobehavioral results of human and animal exposures to adhesive solvents, carbon monoxide (CO), noise, ozone, and pesticides.

Two EPIC IV sessions were devoted to the discussion of environmental issues, the first dealing with clinical toxicology research and the second with experimental toxicology research in animal models. In view of the substantial overlap of issues considered by the clinical and experimental panels, papers from both have been combined in this section. The broad spectrum of issues and insults discussed in these papers defies any simple organization. Therefore, they appear in alphabetical order by senior author. Panelists included:

1. D. Otto (Clinical Panel Chairman), U. S. Environmental Protection Agency, University of North Carolina at Chapel Hill.
2. L. Reiter (Experimental Panel Chairman), U. S. Environmental Protection Agency, Research Triangle Park, North Carolina.
3. R. Dyer, The Johns Hopkins University, Baltimore, Maryland.
4. N. Grandstaff, Stanford University, Stanford, California.
5. L. Grant, University of North Carolina at Chapel Hill.
6. E. Groll-Knapp, Institute for Umvelthygiene, Vienna, Austria.
7. A. Loizzo, Instituto Superiore di Sanita, Rome, Italy.
8. N. Loveless, The University, Dundee, Scotland.
9. J. Pirch, Texas Tech University, Lubbock, Texas.[2]
10. M. Rudnev, Kiev Research Institute of General and Community Hygiene, Kiev, USSR.
11. A. Seppalainen, Institute of Occupational Health, Helsinki, Finland.
12. R. Traystman, The Johns Hopkins University, Baltimore, Maryland.
13. H. Weinberg, Simon Fraser University, Burnaby, British Columbia, Canada.
14. G. Winneke, University of Dusseldorf, Germany.
15. D. Woolley, University of California at Davis.
16. R. Zappoli, University of Florence, Italy.

Neurotoxicity is not a new problem; chemicals adversely affecting the nervous system have troubled mankind since antiquity. For example, one theory (Hammond 1969) postulates that the fall of the Roman Empire was due to lead toxicosis in the ruling class, stemming from the use of lead pipes in the water system. What is new, however, is the systematic study of unwanted effects of toxic agents on nervous system function, i.e., neurotoxicology (cf. Zenick and Reiter, in press). Recent interest in neurotoxicology is largely due to the growing concern over the number of neurotoxicants to which we are exposed in our highly industrialized society. Industrial use of chemicals, the

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[1] Uncited quotations or references to panelists in the following text refer to premeeting correspondence.

[2] Dr. Pirch's paper appears in the Electrogenesis Section.

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increased number of synthetic materials being produced, as well as the large amounts of industrial waste products being introduced into the environment have all added significantly to the problem of neurotoxicology.

The risk of intoxication now extends beyond accidental ingestion and includes occupational and environmental exposure. Examples of the diversity and magnitude of this problem range from the subclinical behavioral manifestations produced by lead intoxication (De la Burde and Choate 1972) to the gross neurotoxicological manifestations recently reported in workers manufacturing the pesticide Kepone (Martinez et al. 1977). Firemen may be at even greater risk from the toxic fumes produced in the combustion of synthetic materials, such as vinyl flooring (Dressler et al. 1975).

The basic objective of both toxicology panels was to evaluate neurobehavioral techniques, particularly ERP measures, as indicators of the adverse effects of environmental insult. Very little direct evidence exists concerning the effects of environmental stressors on ERPs. Few environmental toxicologists are familiar with ERP techniques, and few ERP researchers have addressed themselves to issues of toxicology. We, therefore, face a twofold challenge–to demonstrate the usefulness of ERP measures to environmental toxicologists, while introducing environmental toxicology concerns to other ERP investigators. General methodological factors that affect the choice and utility of neurobehavioral indicators of environmental insult (including behavior, neurochemistry, neuropathology, and other bioelectric phenomena) will be considered before discussing ERPs.

Methodological considerations

What factors should be considered in selecting appropriate tests to determine the neurobehavioral effects and assess the risks of environmental toxicant exposure?

One of the first considerations is the known biological effect of the test agent. Does the agent affect the nervous system? It is not uncommon for the toxicologist to encounter an agent with undefined neurotoxic properties. A new substance may be untested and, therefore, may have unknown biological properties, or the toxicity may be established, but with an undefined CNS component. In these instances, it is desirable to conduct a battery of neurobehavioral tests that screen for CNS toxicity. Such "apical" tests would require utilization and integration of several neural systems so that a chemically induced change in any one system would produce a change in the measured endpoint. Obviously, caution must be exercised in interpreting such data since screening tests are designed to detect a change rather than to identify a site of action.

Grant (this section) elaborates theoretical and methodological issues in the design of innovative screening procedures to detect neurotoxicological effects early in development. Neuropathological and behavioral indicators of "functional brain capacity" are important elements in this approach.

A distinction must be drawn between a direct effect on the nervous system and an indirect change in nervous system function resulting from peripheral effects of a toxicant. The complex role of the nervous system in maintaining the organism's *milieu interieur* makes it possible to detect early toxic manifestations in an organism by utilizing neurobehavioral indices, even when the changes may be secondary to a peripheral effect. Since there are few toxicants that act on a single target organ, the nervous system may provide for early detection of the impending toxicity.

Our greatest interest, however, is in the study of direct toxicant interactions with the nervous system. We will limit our definition of neurotoxicants to those agents acting directly on the nervous system, bearing in mind that it is sometimes difficult to establish this relationship and sometimes advantageous to study indirect effects of toxicants on nervous system activity.

Once an agent has been shown to be neurotoxic, several determinations are required, and each determination is likely to place certain restrictions on the testing methodology. The objectives include:

1. Establishment of dose-response relationships.
2. Determination of the extent of CNS involvement.
3. Determination of the mechanisms responsible for the neurotoxicity.

The primary objective of neurotoxicology is to create a data base for the evaluation of potential health hazards associated with exposure to environmental pollutants. The above determinations, therefore, are critical. The better we understand the biological effects of a toxicant, including its mechanism of action, the better we can define the risks involved in exposure. Such information will then permit the establishment of realistic environmental and occupational exposure standards. The standard-setting process requires the determination of dose-response data, especially at low levels of exposure. However, when we attempt to determine threshold levels, we must, by definition, work at the level of biological noise such that variability from sources other than the experimental manipulation begin to mask any treatment effects (Burt 1975). It is important, then, to develop and utilize testing procedures with maximum sensitivity. Obviously, an understanding of a toxicant's mechanism of action facilitates the choice of methods for threshold determinations.

Problems associated with the administration and duration of toxicant exposure also affect the choice and utility of a particular neurobehavioral index. Consideration must be given to the treatment, duration, age at treatment, and time of testing relative to treatment. These aspects of experimental design place considerable restrictions on testing methodologies. Perinatal exposure to an environmental pollutant, for example, precludes the establishment of a pretreatment baseline and thus places certain demands on the response variability. This exposure regimen would disqualify testing methods that do not permit intergroup comparisons. Similarly, a response that is unstable over time would be an unlikely candidate for chronic toxicity studies, although it may be quite useful for testing acute intoxications.

These factors may seem elementary and are mentioned only to provide a framework for discussion. Neurotoxicology is still in its infancy and the data available on neurobiological effects of toxicants have had little impact on governmental policy decisions related to exposure standards. Greater impact will come only with a better understanding of both the methods employed and the results obtained.

Eastern European countries have, for some time, utilized neurobehavioral data in determining environmental and occupational standards. This fact may account, to some extent, for the generally lower exposure standards in these countries. Rudnev et al. (this section) describe neurobehavioral methods used by the Kiev Institute of General and Communal Hygiene to evaluate the harmful consequences of environmental agents. The Kiev Institute employs both classical behavioral and evoked potential methods to characterize the effects of toxicants.

What are the comparative sensitivity and utility of behavioral, biochemical, neuropathological, and neuroelectric measures of environmental insult?

Sensory deficit can be reliably assessed in many cases by simple tests of sensory threshold (e.g., audiometry and eye chart tests). The effect of environmental toxicants on CNS function, in fact, has been inferred from behavioral measures such as visual threshold (McFarland et al. 1944) or psychophysical discrimination of time intervals (Beard and Wertheim 1967). Neuroelectric measures offer more direct, noninvasive measures of CNS function. Furthermore, the effectiveness of behavioral measures may be compromised by language or motor deficits in some instances (e.g., preverbal children or injured patients), necessitating neuroelectric assessment. The relative sensitivity of behavioral and neuroelectric measures is thus an important issue in environmental toxicology and medicine.

The functional significance of ERP changes can be inferred from concomitant alterations in behavioral measures. What if ERP changes are observed in the absence of behavioral effects? Winneke et al. (this section) describe an interesting dissociation of behavior and the auditory evoked potential (AEP) in studies of alcohol and trichloroethylene (TCE). TCE exposure decreased P2 amplitude of the AEP, but failed to produce any vigilance decrement. Alcohol, on the other hand, impaired vigilance without any effect on the AEP. Winneke et al. discuss the problems of establishing the reliability and validity of these neurobehavioral measures.

Grandstaff and Beard (this section) describe another intriguing dissociation of behavioral and electrophysiological measures: 0.4 ppm ozone exposure produced no observable change in visual evoked potentials, but this exposure did produce a significant *improvement* in vigilance performance. This finding contrasts with a substantial body of evidence that ozone impairs pulmonary function (cf. Stokinger 1954). Orthogonal data derived from behavioral measures can provide useful information concerning the functional significance of observed changes in other physiological measures. In this case, for instance, improved vigilance performance might have been due to an irritant effect of ozone, which counteracted the usual decrease in arousal across time. There is less reason to expect changes in ERP parameters, however, when the CNS is not the primary target organ of the test substance.

Biochemical assays of toxicant levels in the blood, urine, or various tissues of the body are necessary to determine the ultimate distribution and metabolic fate of a test substance. Clinical decisions concerning therapeutic intervention in humans are often based on biochemical measures–e.g., chelating agents may be administered if blood lead levels exceed a certain criterion level. Most biochemical measures, however, are invasive and some (e.g., brain tissue assays) may require the sacrifice of test animals. Animal models are thus necessary to study the mechanisms underlying the effects of neurotoxicants. Although behavioral and neuroelectric measures may provide rapid, simple, reliable, and noninvasive indices of neurotoxic effects, these measures must be coordinated with biochemical measures in order to determine the underlying mechanisms. Furthermore, electrogenesis of ERPs reduces ultimately to a neurochemical process (cf. reviews by Libet, Marczynski, and Somjen, this volume). As Dr. Lipton noted in his opening remarks, the "plumbers and electricians" of the brain must work together to resolve many of the critical questions in neurotoxicology.

The work of Woolley and Reiter (this section) provides a good example of the coordinated assessment of electrophysiological and biochemical parameters. These investigators compared the effects of the insecticide parathion on visual evoked potentials (VEPs) and acetylcholinesterase (AChE) inhibition in rats and monkeys. The latency of VEP components increased markedly 2 to 4 hr after parathion administration in the visual cortex of rats (4 to 8 hr in monkeys) and returned rapidly to pretreatment levels within 8 hr (24 to 48 hr in monkeys). Complete recovery of brain AChE activity, however, required 2 to 4 weeks in rats and extended periods in monkeys. The authors discuss possible mechanisms of functional tolerance to AChE inhibition suggested by the dissociation of electrophysiological and biochemical measures.

A number of papers in this section provide data on the comparative utility of different neuroelectric measures. Seppalainen found the somatosensory evoked potential (SEP) slightly more sensitive than peripheral nerve conduction velocity in assessing the effects of occupational lead exposure. Groll-Knapp et al. reported that the SEP was sensitive, the AEP less sensitive, and the VEP insensitive to CO anoxia. Winneke et al. found the AEP insensitive to the effects of CO exposure, although Winneke and Kastka (in press) previously reported a decrease in the P2 component of the AEP following TCE exposure. Zappoli et al., however, did not find the CNV or SEP as useful as routine electroneuromyographic and EEG examinations for diagnostic signs of subclinical neuropathy in workers exposed to industrial solvents. Zapponi et al. illustrate the utility of yet another EEG measure, spectrum analysis, in the assessment of methyl-parathion poisoning.

The comparative utility question has been posed from an experimental perspective. In the environmental medicine, this question takes a different form, as discussed below.

Which neuroelectric measures provide the best diagnostic and prognostic signs in the clinical assessment of acute and chronic toxicant effects?

There are, of course, no simple answers. The utility of any given measure depends on complex variables, including the extent of nervous system function affected, the question of whether the toxicant exerts a specific or nonspecific effect on CNS function, and the dose and duration of toxicant exposure. That is, the relative utility of different neuroelectric measures must be determined empirically for each environmental toxicant. Unless the specific target system in the nervous system is known, multiple measures should be used to screen for effects in different brain systems and functions.

The value of the comparative approach is exemplified in CO research. Dyer and Annau (this section) studied the effect of CO on visual evoked potentials recorded in the superior colliculus of rats. No effect was observed below 20% carboxyhemoglobin levels, a point at which humans begin to perceive physiological symptoms (cf. Stewart 1975). Results of Groll-Knapp et al. also point to the insensitivity of the visual system, but suggest marked effects in the somatosensory system. Assessment of a single sensory modality may thus provide an incomplete and misleading picture of altered CNS function. We will return to this point later.

What are the comparative effects on ERPs of environmental toxicants, stimulants, and depressants?

Although there is a paucity of evidence concerning the effects of environmental toxicants on ERPs, the effects of many stimulant and depressant drugs on ERPs have been studied (cf. Ashton et al. and Thompson et al., this volume). Drug effects can thus be used as models for comparison with toxicant effects. Winneke et al. (this section) compare the effect of alcohol, a well-known CNS depressant, with TCE. This approach provides a useful frame of reference for calibrating human performance, as well as ERP changes, during exposure to stressors.

How well do subjective ratings correlate with behavioral and ERP measures during exposure to environmental stressors?

Subjective perception of discomfort during toxicant exposure may produce significant, although nonspecific, effects on performance and CNS function (e.g., irritation of the mucosa by ozone may increase arousal). Several panelists (Groll-Knapp, Otto, Winneke) routinely use subjective rating scales in an effort to detect and quantify such effects. Loveless suggests that "annoyance" related to the "perceived loudness" of noise bursts may be a critical variable determining performance decrement in noise studies. The transitory effects of noise bursts on performance could parallel a decrease in subjective loudness and annoyance. Loveless (this section) speculates that ERPs might provide an objective correlate of "perceived noisiness."

Many of the papers in this section deal with the neurobehavioral effects of specific environmental insults rather than methodological issues. The remainder of this summary is devoted to questions concerning the neurobehavioral effects of two common stressors, noise and carbon monoxide.

Neurobehavioral effects of noise

Noise is an environmental stressor that can disrupt cognitive function under certain conditions. Furthermore, noise is omnipresent in urban and industrial environments, where other toxicants are likely to be encountered. Thus, the neurotoxicological effects of noise *per se,* as well as the synergistic (or confounding) effects of noise in combination with other environmental agents, merit careful study.

What are the neurotoxicological consequences of intermittent and continuous noise?

Psychological research on noise has concentrated on effects of continuous high-intensity noise on tasks requiring sustained attention (Broadbent 1971). Continuous white noise at intensities above 90 dB produces a consistent decrement in vigilance performance, which Broadbent attributes to overarousal, although the exact mechanism is poorly understood.

Loveless (this section) notes that the focus on continuous noise has diverted attention from intermittent noise, which might well produce neurobehavioral deficits at lower intensities. He proposes that the effects of intermittent noise can be conceptualized in terms of orienting and defensive reactions "operating through mechanisms of perceptual selection". Noise bursts of moderate intensity, for instance, should evoke a transitory *orienting response* that rapidly habituates. Intense bursts, on the other hand, ought to produce a nonhabituating *defense response*, characterized by reduced sensory intake or reduced sensitivity. The defense response might entail peripheral or central gating of sensory input. Predictions can be made and results interpreted within the framework of Sokolovian theory and the growing body of ERP evidence concerning selective attention and information processing (cf. Tueting, this volume).

Theoretical interest in noise bursts and the orienting response stems from recent work at Dundee. In studies of simple reaction time performance, Loveless and Stanford (1974a,b; 1975) differentiated two components, an early orienting response (O-wave) and a later anticipatory response (E-wave), which may summate in the CNV. These results raise methodological questions with regard to short interstimulus intervals. Loveless warns that "CNV research seems to have fallen into the trap that classical conditioning was in, before it was realized that the use of a short 'optimal' interval confounds orienting responses to the conditional stimulus with anticipatory response. . .my own work, like that of Weerts and Lang (1973), strongly suggests that slow potentials similarly show orienting and anticipatory phases, which are clearly distinct when the ISI is long, but summate when it is short."

Loveless reviews noise research from behavioral and ERP perspectives and relates the data to basic issues in the broader field of stress research. He also describes preliminary evidence of the effects of intermittent noise on ERPs and performance during simple and selective RT tasks. Otto and Benignus (this section) report increased errors and decreased amplitude of the N110 component in a numeric monitoring task during low frequency (11.5 to 350 Hz at 80 dB) noise. Weinberg et al. (this section) failed to observe any detrimental effect of either a "real-life" noise (telephone ring) or artificial (white) noise on the CNV.

Neurobehavioral effects of low-level CO exposure

CO is a colorless, odorless asphyxiant gas that binds tenaciously to hemoglobin in red blood cells to form carboxyhemoglobin (COHb). CO produces anoxic stress by reducing the oxygen-carrying capacity of the blood and impairing the release of oxygen to body tissues.

What is the threshold level at which CO produces an observable decrement in behavioral function?

U. S. air quality standards for CO are 35 ppm (1 hr) and 8.7 ppm (8 hr) in nonindustrial environment (U.S. EPA 1971). These stringent standards are based, in part, on behavioral deficits reported to occur at 2 to 5% COHb (Beard and Wertheim 1967). Three other laboratories (O'Donnell et al. 1971a; Stewart et al. 1973; Otto et al., in press), however, have been unable to replicate the impairment in temporal discrimination reported by Beard and Wertheim. The effect of CO on vigilance performance is likewise equivocal: Horvath et al. (1971), Fodor and Winneke (1972), and Groll-Knapp et al. (1972) reported vigilance decrements below 5% COHb, but subsequent efforts by each of these laboratories to replicate the earlier experiments have failed (Christensen et al. 1977; Winneke et al. and Groll-Knapp et al., this section). CO effects observed by Otto et al. (this section) in a continuous performance vigilance task were marginal. Stewart (1975) has concluded that observations of behavioral decrements at COHb levels below 5% "must be considered suspect" until independently replicated.

Is general arousal level a critical variable mediating the effect of CO on ERPs and behavior?

Beard and Grandstaff (1975) noted that performance decrements associated with low-level CO exposure have only been observed in very monotonous tasks under low arousal-conditions. Arousal level, moreover, has not been adequately controlled in studies reporting negative results. Grandstaff emphasized that general arousal level was probably "the most important variable to be considered in designing or evaluating any study with CO." She proposed a simple test of the CO-arousal hypothesis: sample background EEG throughout the exposure period to determine if activation levels change as a function of COHb concentration. Fast-Fourier analysis techniques can then be used to quantify the frequency content of EEG samples. Haider et al. (1976) reported a slight decrease in alpha accompanied by increased theta and beta activity following 4 hr exposure to 200 ppm CO. This finding is not impressive, considering that COHb levels should have reached at least 15%. Other EEG studies of CO reviewed by Dinman (1969) reported inconsistent or negative results.

Measurement of motor activity level constitutes an alternative or concomitant method of testing the CO-arousal hypothesis. In view of the inconsistent findings of EEG and behavioral studies in the past, both indices of CO effect should be examined concurrently in future studies.

Winneke et al. (this section) directly tested the CO-arousal hypothesis. "Monotony" was varied by changing target probability (0.03 vs. 0.1) and by providing rest breaks with performance feedback during the "less monotonous" condition. Random clicks were superimposed on the vigilance task to obtain AEP measures. Each subject repeated the experiment under 0, 100, and 200/150 ppm CO, conditions that yielded terminal COHb values of 7.5% and 11.3% for low and moderate CO conditions. They did not find any effect of CO exposure on vigilance performance or AEPs. In order to rule out the possibility that random clicks enhanced arousal, Winneke et al. ran 20 additional subjects without clicks. Results were the same and thus do not support the CO-arousal hypothesis.

Groll-Knapp et al. (this section) used a classical, straightforward method to minimize arousal: a sleep study was undertaken to avoid the uncontrollable variability caused by voluntary shifts of attention during waking. Exposure to 100 ppm during 7 hr of sleep increased the amount of stage 3 and 4 sleep, but decreased rapid eye movement (REM) sleep. All components of the AEP shifted in a positive direction during stage 4 sleep. Groll-Knapp et al. emphasize that CO effects are more consistent during sleep than waking and recommend this approach as an effective method of controlling arousal in toxicant research.

Are the neurobehavioral effects of CO modality-specific?

Xintaras et al. (1966a,b) described changes in flash evoked potentials in the superior colliculus of rats following exposure to 50 ppm CO. Dyer and Annau (this section) did not observe any significant changes below 20% COHb in an attempted replication of the Xintaras experiment. Reasons for the discrepant results are unclear, although several strands of evidence suggest that visual function, at least in the photopic range, is not particularly susceptible to CO impairment.

Parameters of visual function reported to be impaired at 3 to 20% COHb levels include brightness thresholds (McFarland et al. 1944; Halperin et al. 1947, 1959; Beard and Grandstaff 1970), visual acuity (3 to 10% COHb: Beard and Grandstaff 1970), and dark adaptation (17% COHb: McFarland et al. 1972, McFarland 1973). On the other hand, COHb levels below 20% do not appear to affect brightness discrimination (Ramsey 1972, 1973; Weir and Rockwell 1973), depth perception (McFarland et al. 1972; McFarland 1973; Ramsey 1972, 1973; Wright et al. 1973), glare recovery (McFarland et al. 1972, McFarland 1973; Wright et al. 1973), or critical flicker fusion (CCF) (Fodor and Winneke 1972, Guest et al. 1970, Johnson et al. 1974, O'Donnell et al. 1971a, Ramsey 1973). Beard and Grandstaff (1970) did a marginal decrease in CCF at 3 to 10% COHb levels.

Groll-Knapp et al. (this section) compared the effects of low-level CO on auditory, visual, and somatosensory EPs. As noted previously, the VEP was insensitive to CO effects. Other evidence also suggests differential sensitivity of auditory and visual function to CO impairment. Beard and Wertheim (1967) demonstrated a CO dose-related decrement in the estimation of tone duration, an effect that Beard and Grandstaff (1970) were unable to reproduce in the visual modality.

Results of other experiments employing visual stimuli are also inconsistent. Horvath et al. (1971) observed a significant performance decrement in a visual vigilance task following 2-1/4-hr exposure to 111 ppm CO. Winneke et al. (this section) and Christensen et al. (1977) both failed to replicate the Horvath et al. study. Otto et al. (this section), on the other hand, observed CO-related changes in CNV and N1P1 components during a visual monitoring task. Further comparative studies of CO effects on different parameters of auditory, somatosensory, and visual function are needed to resolve the inconsistencies of existing data and to identify the mechanisms by which CO impairs sensory function.

Luminance level is an important parameter of visual function that could possibly account for discrepant results in CO studies employing visual stimuli. At high levels of luminance, photopic vision is mediated by a dense population of cones in the fovea, while at low levels, scotopic vision is mediated by a much less dense population of rods distributed more uniformly throughout the retinal field. McFarland et al. (1944) showed that hypoxic hypoxia affected visual acuity much more at scotopic than photopic levels of illumination. Merigan and Blick (1978) and Evans and Garman (1978) have argued, on the basis of relative neuronal density and redundancy, that scotopic vision is probably more susceptible than photopic vision to neurotoxicant effects. Winneke et al. (this section) point out that they used a higher luminance level than Horvath et al. (1971) used, and suggest that this factor could possibly explain the lack of CO effects. Further study is needed to clarify the relationship of CO exposure, luminance level, and visual function.

What are the short-term compensatory and long-term adaptive mechanisms of response in man to low level CO stress?

The behavioral muddle of CO research suggests that the critical variable controlling CO effects has not yet been identified. Activation of a physiological compensatory mechanism was proposed as a possible explanation of negative findings by Fodor and Winneke (1972). The paradoxical effects observed in some studies of behavioral decrements early in the uptake cycle, followed by a return to normal performance at higher COHb concentrations, support this speculation. Beard and Grandstaff (1975), for example, observed "a definite trend for CO to have its greatest effect during the initial portion of the uptake period shortly after it was introduced (within 30 min.). Therefore, if the impairment in performance of a given task is slight, or occurs primarily during the uptake stage, this effect would easily be obscured."

What is known about the physiological reaction of the organism to CO? The cardiovascular system responds to anoxic stress by increasing cardiac output or selectively increasing blood flow to specific organs. Patients with impaired oxygen-uptake capacity (e.g., coronary artery disease) are thus uniquely susceptible to CO poisoning (Ayres et al. 1969, Aronow and Isbell 1973, Anderson et al. 1973). Paulson et al. (1973) reported that cerebral blood flow increased at moderate (20%) COHb levels in humans. Traystman and Carlson (1974) extended this work in rats to show that cerebral vasodilation results from both CO hypoxia and hypoxic hypoxia at comparable arterial 0_2 levels. This evidence indicates that the brain can effectively compensate for the oxygen deficiency produced by CO anoxia at levels up to about 20% COHb. The conditions that control the onset threshold of this mechanism, however, have not been established.

Determination of threshold conditions could provide a key to the contradictory behavioral findings obtained during low-level CO exposures. If cerebral vasodilation does not occur until COHb levels reach 5%, subtle behavioral measures may show effects at 2 to 5% COHb. If the compensatory mechanism triggers at 5% COHb, then performance should rapidly return to control levels. Fodor and Winneke (1972), Beard and Grandstaff (1975), and Otto et al. (this section) have observed such paradoxical findings. Research on cerebral hemodynamics (Traystman, this section), however, provides no direct evidence of any lower threshold triggering of the cerebral compensatory mechanism.

Grandstaff suggested that behavioral as well as physiological compensatory mechanisms may counteract the effect of CO. Behavioral reactions might take the form of head-shaking, eye-blinking, or squirming around to restore alertness as the subject perceives himself becoming drowsy. Grandstaff further pointed out that activity levels of subjects ought to be measured along with other electrophysiological and behavioral measures. EOG, EMG, or other kinds of electromechanical transducers could be used for this purpose. Activity levels constitute a standard measure of toxicant effect in animal studies. Measurement of activity levels in humans could provide a useful bridge for extrapolation from animal to human research.

Grandstaff also raised the question of adaptation in relation to the compensatory response of the organism to CO. The time course of adaptation to low levels of CO has not been systematically investigated in humans, particularly in relation to performance on specific tasks. (Smokers are generally rejected from CO studies on the assumption that adaptation to elevated COHb levels does occur.) Adaptation to the hypoxic conditions of living at high altitude is well documented. Adaptation to CO is an important question for further study.

Conclusions

Neurotoxicology is an emerging discipline devoted to the study of the adverse effects of environmental insult, both physical and chemical, on nervous system function. The issues addressed in this review and the papers that follow are primarily methodological questions dealing with the comparative utility of available neurobehavioral measures of toxicity. The application of ERP techniques in the assessment of environmental insult has been limited, although the results of several studies in this section suggest that certain ERP parameters are sensitive indicators of neurotoxicant effects. Interpretation of the functional significance of observed ERP changes presently requires the concomitant recording of behavioral or other neurobiological criterion measures. As our understanding of the neurophysiological and neurochemical substrates of ERPs grows, these measures should provide an increasingly important index of the neurobehavioral consequences of exposure to environmental stressors.

H. E. Stokinger, Chairman of the Threshold Limits Committee at the National Institute of Occupational Safety and Health, has stated that "changes in the visual evoked response (VER) are presently not sufficiently well understood in overall physiological terms to serve as basic criteria for air standards" (1974, p20). Although the neuroanatomical substrates and functional significance of many ERP components are presently unknown, ERPs do offer a convenient, noninvasive window on central nervous system activity. If appropriate precautions are taken to avoid extracerebral artifacts, changes in ERP latency or amplitude induced by environmental agents should provide a legitimate and useful index of the effect of toxicant exposure on brain function (cf. Otto, in press, for extended discussion of this issue). The fact that the precise *mechanisms* underlying ERPs may not be completely understood is essentially irrelevant to the use of these bioelectric events as measures of neurotoxicant *effects.*

This volume and others (Donchin and Lindsley 1969; Regan 1972; McCallum and Knott 1973, 1976; Desmedt 1977) document the rapid growth of knowledge in the ERP field. The clinical utility of ERPs has been clearly established in audiometry (Davis 1976), neurology (Starr and Achor 1975), ophthalmology (Sokol 1976), psychiatry (Shagass 1972), and psychopharmacology (Tecce et al. 1978). The remarkable progress in clinical applications in reviewed extensively in Callaway et al. (in press). Thus, the view that ERPs may be mere epiphenomena of brain function (Uttal 1965) and the reluctance to use ERP evidence as criteria for exposure standards are no longer defensible.

CARBON MONOXIDE AND SUPERIOR COLLICULUS EVOKED POTENTIALS[1]

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Attempts to determine the level of carbon monoxide (CO) exposure that produces observable behavioral changes have produced conflicting results. Since evoked potentials (EPs) provide information about the general functional integrity of the sensory system studied, they might be useful in determining the level of exposure to CO that results in changes in neural function. In turn, since changes in behavior must be preceded or accompanied by changes in neuronal activity, the EP technique may also be useful in predicting the CO level that can be expected to produce behavioral changes. To this end, Xintaras et al. (1966) recorded flash evoked potentials from both the visual cortex and superior colliculus of unanesthetized rats and reported that the superior colliculus evoked potential (SCEP) was uniquely sensitive to low concentrations of CO. Changes in the SCEP were observed at levels of 50 ppm CO. Procedural difficulties make generalization from this study hazardous. The results were presented in descriptive terms based on a few animals and no effort to control for peripheral variables such as pupil diameter was described. Since pupil diameter can be expected to vary with respect to arousal level and hypoxic condition, and since variations in pupil diameter can be expected to produce variations in both amplitude and latency of the evoked potential, failure to control for it represents a serious shortcoming. The present paper accommodates these shortcomings and reports results of SCEP experiments using short-term (2- to 2.5-hr) exposures to CO in chronically implanted unanesthetized rats.

Methods

Eight adult male Long Evans rats were used in the experiments. Animals were anesthetized with Equithesin, and bipolar 0.25-mm twisted nichrome wires were lowered into the superior colliculus under stereotaxic guidance. Tips of the electrodes were separated from each other in the vertical plane by 1 mm, and the electrodes were lowered into the SC 5.5 mm posterior to bregma, 1.5 mm lateral and 3.8 mm below the cortical surface, according to the atlas of Skinner (1971). Electrodes were cemented in place with dental acrylic and connected to an Amphenol receptacle. A 0-80 stainless steel screw was inserted into the skull over the frontal sinus and connected by an insulated nichrome wire to the receptacle for purposes of grounding the animal. At least 1 week of recovery was allowed before any recordings were made.

After pupils were dilated with atropine sulfate and the animals were connected to the recording apparatus via an Amphenol plug and Microdot mininoise shielded cable, they were placed in a chamber 8 cm wide, 20 cm long, and 38 cm high, which had mirrors on three walls, ceiling, and floor. The fourth wall was clear Plexiglas, and had a Grass PS-2 photostimulator lamp mounted flush against it. Either air or a mixture of air and CO was blown into the chamber at 6 liters/min through a 0.6-cm hole 5 cm from the floor. Throughout the experiment the chamber was illuminated by overhead lights in the laboratory, yielding a luminance of about 100 millilamberts.

Recordings were made with high- and low-frequency filters set at 10 kHz and 0.2 Hz, respectively. Amplified signals were led to an oscilloscope for monitoring, and to a PDP-8 or PDP-12 computer for averaging. The poststimulus analysis epoch was 240 msec, each millisecond representing one bin of a 240-point plot display. Voltage was sampled every 333 μsec, and the three samples taken each millisecond were averaged to produce the value deposited in a given bin. A signal from the computer triggered a Grass S44 stimulator, which in turn triggered the photostimulator. The photostimulator was set at its

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[1] This work was supported by Fight for Sight grant-in-aid, G-553, HL 05453 and EHS 00454.

highest intensity, which produced a 10-μsec flash of about 1,500,000 candle power.

Averaged responses were displayed on an oscilloscope, and a cursor controlled by the teletype and one analog channel printed the latency to the nearest millisecond and amplitude to the nearest microvolt for any bin requested. The displayed signal could be photographed with a Polaroid camera or printed by a Centronics printer. The printouts were dot plots with numeric descriptors of each dot.

Desired concentrations of CO were mixed in a large drum, continuously monitored with a Beckman infrared analyzer, and pumped into the recording chamber.

The experimental paradigm consisted of recording the response to 500 flashes presented at 0.5 Hz while air was blown into the chamber. The air was then replaced with the desired concentration of CO, the animal allowed 2 hr to equilibrate, and the series of flashes repeated. No systematic attempts were made to measure activity during this period, but the animals were observed to be generally quiescent. Latencies of peaks P1, N3, P3, N4, N5, and P5 and peak-to-peak amplitudes of N1P1, P3N4, N4P4, P4N5, and N5P5 were then expressed as a percentage of the pre-exposure values, a procedure that minimizes the interanimal differences known to occur in bipolar recordings from the SC (Dyer and Annau 1977). These experiments were performed with 1000, 500, 250, 150, and 0 ppm CO. All conditions were presented to each animal in random order with at least 1 week between sessions. A repeated measures analysis of variance was performed separately for each component analyzed, and individual comparisons were made using the t-test technique.

Carboxyhemoglobin (COHb) saturations at the different exposure levels were determined in a separate series of rats from the same strain with chronically implanted venous catheters using the methods of Weinstein and Annau (1967) and Small et al. (1971).

Results

COHb saturations reached equilibrium before 120 min of exposure in sedentary rats. Values of 13, 22, 38, and 55% were found to result from exposures to 150, 250, 500, and 1000 ppm.

Fig. 1 shows a typical SCEP with the different peaks identified. Low levels of exposure to CO increased the amplitude of late components, but did not affect early components. Severe exposure (1000 ppm) depressed amplitudes of late components and increased all latencies.

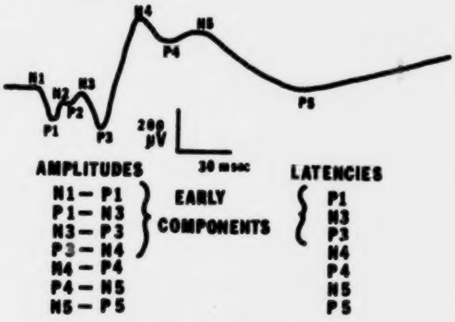

Fig. 1. Superior colliculus evoked potential.

The only significant departures from compressed air values occurred at exposures to 500 and 1000 ppm. At 500 ppm, there were significant increases in P3N4 and N4P4 amplitude. At 1000 ppm, there was a significant depression in both P3N4 and N5P5 amplitudes, and a significant increase in latency of P1, N3, P3, N4, and P4 peaks. At all concentrations, there was marked interanimal variability, not only in magnitude but in some cases even in direction of effect.

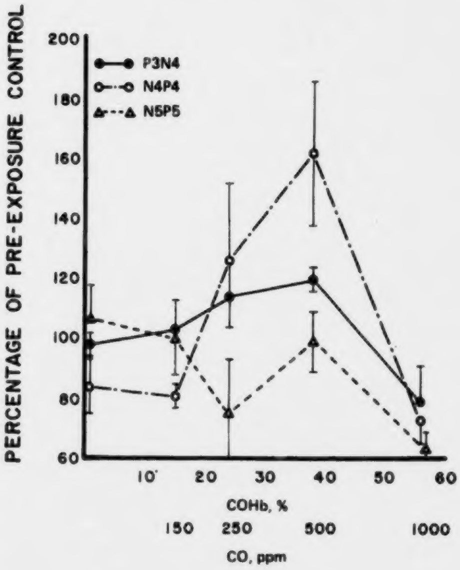

Fig. 2. Effects of CO on superior colliculus evoked potential amplitudes.

Fig. 2 and 3 show the effects of varying concentration of CO upon amplitude and latency of different peaks. These figures indicate that amplitude is more sensitive than latency as a measure of CO toxicity.

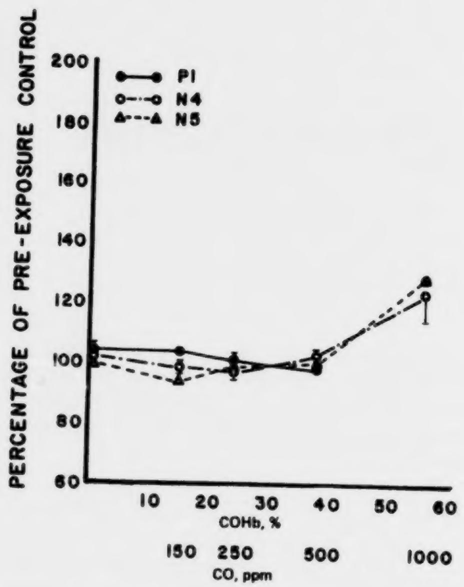

Fig. 3. Effects of CO on superior colliculus evoked potential latencies.

Discussion

The present results show that 150 and 250 ppm concentrations of CO, which produced COHb levels of 13 and 22%, do not significantly change the SCEP. These results are contrary to those of Xintaras et al. (1966) who reported EP changes at 50 and 100 ppm. A number of explanations for the discrepancy are possible. Dyer and Annau (1977) have shown that it takes at least 2 hr for dark adaptation to occur when rats are placed in a recording chamber darker than the home cage. During this time, repeated flashing elicits EPs of greater and greater amplitude. Further observations from our lab suggest that even when no dark adaptation occurs in the course of an experiment, there is an increase in amplitude of several components from the first block of 50 to the second block of 50 trials. Thus, the increased amplitudes observed by Xintaras et al. (1966) during exposure to low CO levels may have reflected adaptation phenomena. The interanimal variability observed in the present experiment indicates, furthermore, that descriptive findings from a small number of animals may be very misleading.

The finding that a concentration of 500 ppm CO significantly increases EP amplitudes is of interest. It is well known that the electrical activity of the nervous system during the course of anoxia progresses through a stage of relative increased activity. EP amplitudes increase, spontaneous cell firing increases, and the EEG is characterized by low-amplitude, high-frequency waves (Baumgartner et al. 1961). At least three mechanisms may be postulated to account for this phase of activation: greater sensitivity of inhibitory neurons to hypoxia (Gelfan and Tarlov 1955), activation of carotid body chemoreceptors by low arterial 0_2 pressure with subsequent reticular and cortical activation (Dell and Bonvallet 1956), and partial depolarization induced by electrolyte shifts known to occur during hypoxia (Michael 1973). Finding the activation phase with exposures to 500 ppm CO appears to rule out the chemoreceptor hypothesis since the chemoreceptors are presumably not activated at this CO concentration. Electrolyte shifts cannot account for the activation either, since they are also presumed not to occur during CO exposures (DeValois and Schade 1967). Thus, the most plausible explanation appears to be a release from inhibition produced by a greater sensitivity of inhibitory synapses to hypoxia.

Traystman (this section) has shown that cerebral blood flow in dogs increases markedly to compensate for reduced blood oxygen under conditions of both CO hypoxia and hypoxic hypoxia. Moreover, Traystman's data indicate that brain oxygen consumption remains relatively stable up to 30% COHb, but begins to decrease at an undefined point between 30 and 51% COHb. If one can generalize from dog to rat, then the clear depression of SCEP components observed at 1000 ppm (55% COHb) may be attributed to decreased oxygen consumption of the brain at high COHb levels. The increase of SCEP components observed at 500 ppm CO (38% COHb), however, cannot be attributed to a decrease in oxygen consumption and may, in fact, reflect activity of the presently unknown compensatory mechanism that mediates cerebral blood flow. Further study is required to elaborate the relationship of EP changes, cerebral blood flow and oxygen consumption, and the compensatory response of the brain to CO hypoxia.

EFFECTS OF OZONE ON HUMAN CENTRAL NERVOUS SYSTEM FUNCTION[1]

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The purpose of this study was to assess the effects of exposure to low levels of ozone on CNS function in humans. Twenty young, adult, paid volunteers were assigned to experimental or control groups of 10 subjects each. All subjects completed four 4-hour testing sessions on successive days as follows: day 1: orientation; day 2: pre-exposure baseline; day 3: ozone exposure (experimental group only); and day 4: post-exposure baseline. Subjects in the experimental group were exposed doubleblind to 0.4 ppm (800 $\mu g/m^3$) ozone for 4 hours in a small audiometric booth on day 3.

The following parameters were measured during each testing session: errors and response latency in detecting target lights in a peripheral vision testing device (Grandstaff 1974), respiration rate, EEG, and CNV. Clinical measures of peripheral (Goldman Perimeter) and central (Tangent Screen and/or Goldman Perimeter) fields and dark adaptation (Goldman Adaptometer) were also obtained before and after each testing session.

Subjects exposed to ozone made significantly fewer errors and responded more rapidly to target lights on day 3 than subjects not exposed to ozone. This effect was generalized throughout the peripheral field. Ozone exposure did not produce any significant change in clinical measures of peripheral or central fields, visual thresholds, or in respiration rates. The EEG/CNV analysis was inconclusive. The observed behavioral change may reflect a general increase in arousal level from the stress induced by ozone exposure.

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NEUROBEHAVIORAL ASSESSMENT OF EFFECTS OF ENVIRONMENTAL INSULTS EARLY IN DEVELOPMENT

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This paper focusses on neurobehavioral assessment of toxicity following environmental insults early in development. More specifically, theoretical and methodological considerations providing a rationale for development of a neurotoxicity screening approach for detection of early developmental insult effects are discussed, with primary emphasis on the use of neuropathological and behavioral testing methods. Within that context, the question of the relative sensitivity of such assessments for detecting neurotoxicity is considered and recent efforts aimed at improving neuropathological screening procedures are noted. It is hoped that raising the issue of relative sensitivity of neuropathology and behavioral screening approaches will stimulate discussion on (1) how electrophysiological methods might be employed to augment neuropathological and behavioral assessments of neurotoxicity following insults early in development and (2) what special problems are apt to be encountered in trying to employ electrophysiological techniques in that manner.

Assessment of changes in "functional brain capacity" is a key theoretical issue implicitly addressed by most studies of neurotoxicity. Functional brain capacity, reflecting the number of functionally intact neurons in the central nervous system (CNS), number of functionally intact synaptic connections, and the integrity of neurochemical processes, determines the maximum complexity of neurobehavioral responses mediated by the CNS of an organism. As indicated in Fig. 1, functional brain capacity is thought to increase prenatally and neonatally with the rapid proliferation of neural tissue during early development. It likely asymptotes sometime after puberty, reflecting offsetting effects of normal neuronal cell losses and gains in processing efficiency with experience. In old age functional capacity gradually decreases as the effects of cell losses predominate and lead to the manifestation of neurobehavioral deficits defined as "senility" or "senescence". Even very small excess rates of neuronal cell losses of less than 0.1%, if induced by environmental insult early in development, could lead to substantial reductions in rate of maturation and ultimate maximum level of functional capacity attained. Or the effects of early "mild" damage might not be manifested until late in life, when "premature senescence" theoretically could occur, even 10 to 20 years sooner than would otherwise be expected.

For assessment of toxic effects of exposures to environmental agents early in development, such exposures can be restricted to either prenatal or early postnatal periods, or they can be of a more chronic nature, extending throughout these periods and possibly throughout the entire life of the animal. With such exposures, assessments of toxicity can only be undertaken *after* the initiation of the exposure, thus not allowing for accumulation of pre-exposure baseline data against which to compare postexposure effects. This necessitates use of between-subject experimental designs, with longitudinal study of subjects demanded by the nature of the problem in order to detect possible immediate effects of exposures on early development, as well as possible delayed effects not appearing until adult life or old age. Toxicity assessments appropriate at different life stages starting during prenatal exposures include: (1) prenatal evaluations of unborn fetuses for embryotoxicity and teratogenic effects, including neuropathology evaluations of brain damage, (2) periodic sampling of subjects at various life stages postnatally for neuropathology screening, and (3) postnatal development assessments and adult behavioral testing on remaining living subjects.

With high exposure levels for many agents, neural damage is severe enough to be detected by existing routine neuropathology screening procedures. These procedures mainly consist of: (1) gross external examination of the brain for obvious alterations in size, shape, or surface features, for signs of hemorrhage or abscess, or for other indications of abnormality, and

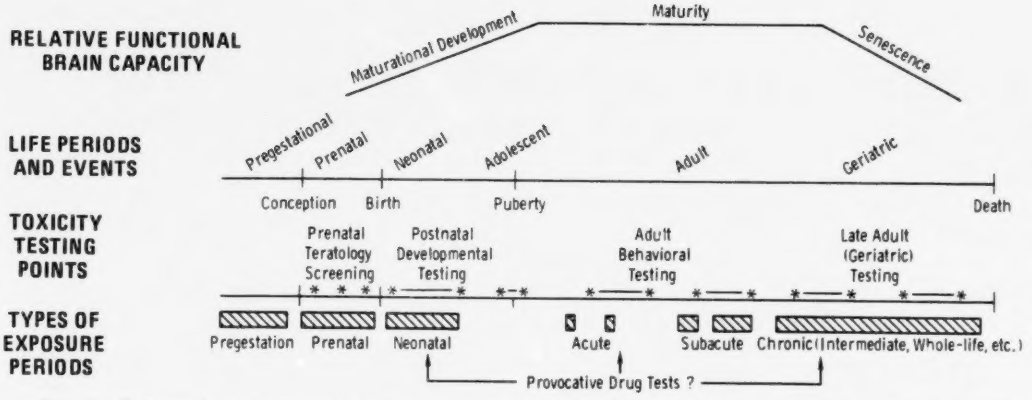

Fig. 1. Schematic representation of conceptual framework upon which are based suggestions for longitudinal designs for behavioral teratology studies. Normal changes in relative levels of functional brain capacity, determining the maximum complexity of neurobehavioral responses and the neural reserve of an organism, are plotted (top) in relation to periods and events occurring during the life span of most mammalian species. Various types of experimental exposure periods are depicted in relation to different points in life when they might be administered to reflect actual types of exposure problems. Toxicity testing points (*), when different types of anatomical and behavioral evaluations are appropriately conducted, are noted in relation to the exposure periods. (From Grant 1976.)

(2) rough serial sectioning to allow scanning for readily observable internal lesions, enlarged ventricular spaces, etc. It has been estimated that at least a 30% loss of neurons in a particular brain area would have to occur before existing standard neuropathology screening procedures could detect such a defect. It thus appears unlikely that such procedures would be adequate to detect small reductions in neuronal density or other subtle changes in brain morphology resulting from low-level exposures to various environmental agents, which are becoming of increasing concern to environmental toxicologists and regulatory agencies.

Efforts aimed at improving neuropathology screening procedures include work by Dr. Martin Krigman at the University of North Carolina in Chapel Hill. His screening procedures attempt to quantify damage to the CNS at both the light-microscope and ultrastructural level. Light-microscope analyses include measurements of cortical mantle thickness and determinations of neuronal density by meticulous counting of neurons in cortical or other brain areas on sections subdivided by grid coordinates for evaluation. On an ultrastructural level, analyses include estimates of density of synaptic contact points in neuropil of cortex or neostriatum by counting of synaptic profiles in electron micrographs from sampled brain regions. These quantification techniques are estimated to be sensitive enough to reliably detect changes of less than 10% in neuronal or synaptic density.

Another morphological approach holding some promise for improved neuropathology screening is the use of histochemical methods for the demonstration of specific catecholamine, indoleamine, or other neurotransmitter-containing neural pathways in the CNS. By employing such methods in my laboratory (Nemeroff et al. 1977), it was possible to demonstrate a marked prolonged reduction in numbers of dopamine (DA) neurons present in the arcuate nucleus of the hypothalamus in rats neonatally treated with monosodium-l-glutamate (MSG), a widely used food additive. The reduction in DA neurons was shown to still exist at time points in the adult life of MSG-treated animals when an early lesion in the arcuate nucleus was no longer readily detected with standard neurohistological procedures.

Even with improved neuropathology screening procedures of the type outlined above, certain types of neurotoxic effects may not be detectable morphologically. For example, subtle alterations in neurotransmitter release effects on postsynaptic transmitter receptor sites would not be picked up with improved neuropathology screening and are even difficult to demonstrate biochemically. Presumably, however, such effects or neuronal damage below neuropathology detection limits may be reflected by alterations in behavioral responses mediated by affected neural pathways or biochemical processes. Thus, in addition to neuropathology screening, assessments of toxic effects on behavior would seem to be advisable. In addition, it is here that electrophysiological techniques might also provide an increased level of sensitivity over neuropathology screening methods for detecting subtle alterations in neural function.

As for postnatal developmental assessments and later adult behavioral testing, such relatively expensive and time-consuming procedures should probably be reserved for exposure levels below those producing significant effects detected by prenatal teratology or neuropathology screening procedures. Evaluations designed to assess the progress of maturation early in development might profitably include not only behavioral tests, but also measures of growth and physical development. This allows for estimates of whether behavioral changes likely indicative of altered neural function occur at exposure levels below those producing general effects on growth or maturation of other organ systems. Thus, ages at which certain physical development landmarks appear (e.g., incisor eruption, eye opening, vaginal opening or testes descent) should be recorded. In addition, behavioral assessments would focus early in development on the maturation of certain reflexes (e.g., righting, auditory startle, and visual placing responses), as well as indexing the shift of the immature pattern of ambulation called "pivoting" to the adult pattern of straight-line forward locomotion and the appearance of other behavior patterns (sitting up, grooming, climbing). Kimmel et al. (1978) describe an approach employed collaboratively by several laboratories for assessment of chronic low-level lead exposure effects on early postnatal development, using many different types of behavioral and morphological assessments of toxic effects.

Adult behavioral testing might then proceed in a sequence of increasingly more sophisticated and difficult assessment procedures. The first, and grossest, level of assessment would consist of continuous monitoring for overt signs of toxicity. This would include, in addition to changes in body weight, deterioration of fur condition, observations on abnormal postural or gait characteristics, increased sensitivity to handling, the occurrence of tremor or repetitive stereotyped motor patterns, and loss of reflexes. The second level of testing would involve attempts at quantifying changes in spontaneous behavioral responses such as locomotor activity, food and water consumption, and sex behavior. The third level of assessment would involve analyses of behavior in much more controlled circumstances and would include operant conditoning paradigms to assess an agent's impact on learning and memory functions and/or shifts in sensory processes. Since delayed effects of early insults may not be manifect until late in adult life, one or more components of the above procedure may need to be repeated, especially as subjects approach old age in order to detect premature senescence.

The above testing approach would permit a broad and detailed description of neurobehavioral effects induced by a given agent. It would, however, be very costly and time-consuming, with final results not available possibly for several years if testing during the geriatric period was necessitated by the lack of detected effects earlier in life. Alternatively, for screening purposes in which *any* sign of alteration in neural function would perhaps suffice to warrant the raising of "caution" signals for a given agent, certain heuristics might be adopted, such as (1) following up findings of developmental delays, however small, in maturation of reflexes to see if they are predictive of later, more severe behavior deficits; (2) use of "apical" behavioral tests in which paradigms are employed that require a number of behavioral response systems to be intact for successful performance of the tasks, e.g., operant conditioning paradigms where food or water motivation, motor functions, and learning or memory processes must all be intact to permit performance of the conditioned response(s) at normal levels; and (3) employment of "provocative" drug tests to look for increased vulnerability of performance in exposed animals to deleterious or facilitating effects of neurally active pharmacological agents.

Where electrophysiological techniques might appropriately be employed in the above framework as possible screening procedures for neurotoxicity is a subject for further discussion. Electrophysiological techniques have been applied successfully to the assessment of neurotoxic effects in adult animals exposued to environmental agents (cf. other reports in this section). However, there are inherent methodological difficulties in assessing the effects on subsequent development of prenatal and neonatal toxicant exposure. The utility of electrophysiological techniques as neurotoxicity screening tools in such cases remains to be demonstrated.

NEURO- AND PSYCHOPHYSIOLOGICAL EFFECTS OF MODERATE CARBON MONOXIDE EXPOSURE

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Numerous experiments have been conducted on the effects of CO exposure on human behavior (cf. reviews by Permutt and Farhi 1969, Coburn 1970, USDHEW (1970), and Beard and Grandstaff 1975). Probably due to differences in experimental design and parameter measurement, the effects of CO seem contradictory. Some aspects of human behavior are affected by low COHb levels while others show no impairment until the COHb level is higher. The capacity for continuous observation of weak or infrequent stimuli, as in a vigilance task, can be a sensitive indicator of behavioral impairment while complex psychomotor tasks show no reliable impairment. Beard and Grandstaff (1975) have suggested that failure to demonstrate impairment on a complex task may be due to the intrinsic activating characteristics of the task that possibly facilitate the mobilization of compensatory mechanisms. In the presence of significant changes in behavior, some investigators infer an impairment of CNS function due to increased CO burden. In an effort to determine the mode of CNS impairment, spontaneous EEG activity, EPs, and CNV have been examined.

EEG has yielded no reliable differences during acute exposure to low levels of CO. Zorn (1964), Shul'ga (1964), Stewart et al. (1970, 1973), Hosko (1970), and Groll-Knapp et al. (1972) found no alteration in spontaneous EEG with COHb levels as high as 33%, although Grudzinska (1963) observed an augmented occurrence of slow wave components in the EEG of workers chronically exposed to 100 ppm CO with COHb levels of less than 7%. Additionally, an increased occurrence of flat EEG accompanied by irregular alpha rhythm was noted. In contrast to the absence of EEG changes at high COHb levels. O'Donnell et al. (1971a) found alterations in EEG sleep patterns during exposure to 75 and 150 ppm for 7 hours of nocturnal sleep. A nonsignificant trend toward increased duration of deep sleep (stages 3 and 4) was noted. CO-induced changes were more pronounced but not significant during the early phases of sleep when COHb levels were lower. It was hypothesized that early adaptation mechanisms were stimulated by CO exposure during the initial 3 hr.

The analysis of evoked and slow potentials permits investigation of processes that are more specific than those reflected in the spontaneous EEG. EPs as an indicator of CO-induced functional CNS deterioration in man were first investigated by Hosko (1970). No significant changes in peak latencies or amplitudes of VEPs were found below 15% COHb. With COHb levels between 20 and 22%, an increase in amplitude of the late potential component (70 msec) and a negative-going shift after P120 were described. Due to the small number of subjects in the high COHb group, these results must be regarded with caution.

AEPs in CO experiments were studied by Groll-Knapp in 1971 (unpublished). Experiments using 14 subjects at 0, 15, 100 and 150 ppm exposure for 2 hr showed a consistent, but nonsignificant reduction in amplitudes and a lengthening of peak latencies of late components. The extent of AEP decrement appeared to be proportional to the level of CO exposure.

Slow potentials, which are considered to be CNS correlates of attention, anticipation, and motor readiness, were first used as indicators of CO-induced CNS disturbance by Groll-Knapp et al. (1972). A significant diminution of CNV amplitude during moderate (50, 100, 150 ppm) exposure was found.

EP experiments with animals have yielded contradictory results. Xintaras et al. (1966b) described an increase in superior colliculus (SC) EP in rats exposed to CO levels of 50 ppm. In contrast, Dyer and Annau (this volume) found significant changes in SCEPs only during exposure of rats to 500 and 1000 ppm CO. During exposure to 500 ppm SCEPs were

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[1] With financial support of the Österreichischen Fonds zur Förderung der wissenschaftlichen Forschung and the commission of the European Communities.

augmented, but during exposure to 1000 ppm, SCEPs were decreased in amplitude.

No reliable neurobehavioral effect has been demonstrated for moderate COHb levels. Furthermore, several investigators (cf. Winneke et al., this volume) have been unable to replicate their own findings. This predicament suggests either considerable variability in the sensitivity of different neurobehavioral measures to the hypoxic effects of CO, or that slight changes in experimental design or arousal level can mask the subtle effects of moderate COHb levels. Studies of the comparative sensitivity to CO exposure of different neurobehavioral and electrophysiological measures and exploration of more effective methods for controlling the arousal level of subjects are needed to clarify these issues.

Two experiments pertinent to these questions are reported here. The first study examines the comparative sensitivity of several behavioral (auditory vigilance, simple addition, short-term memory) and neuroelectric (CNV; auditory, somatosensory, and visual evoked potentials; EEG power spectrum) measures during exposure to 200 ppm CO. The second explores nocturnal sleep as a method to control voluntary modulation of attention and arousal.

Experiment 1

Methods

Twenty nonsmoking unpaid volunteers (11 male), aged 18 to 24 yr, served as subjects. Each subject was exposed double-blind to two conditions (0 and 200 ppm CO) in a pneumatic chamber with sessions separated by at least 4 days. Each session lasted 210 min and resulted in a maximum COHb level of 12%. COHb levels are determined spectrophotometrically from blood samples obtained after each session. Observed values agreed well with values calculated by means of the Coburn et al. (1965) formula. Subjects completed the tasks twice during each session. For the 200 ppm condition, tasks were administered at a low COHb level (below 6% COHb) and again at a higher level (above 8%).

EEG was recorded on FM tape from Ag/AgCl electrodes at the vertex referenced to linked mastoids. EOG was also recorded for offline editing of eye movement artifact. A CAT 1000 and Sunai Frequency Analyzer were used for off-line data processing. Power spectra (at 4 and 10% COHb) were computed in 10 sec epochs for frequencies of 5 to 15 Hz with subjects at rest. Average power spectra were evaluated for 10 min periods.

An auditory vigilance task was used for CNV assessment. Pairs of 1 msec clicks were presented via earphones with an intersignal interval of 1 sec and an average interpair interval of 4.17 sec. The intensity of both stimuli was equal (96 dBA) for irrelevant pairs, while the intensity of the second stimulus was slightly less (93 dBA) for relevant pairs to which subjects were required to respond. The vigilance task consisted of three continuous series, each containing 41 relevant and 200 nonrelevant pairs. CNVs were selectively averaged for hits, misses, and irrelevant pairs using a 4 sec sweep rate and N=100. CNV amplitude was measured as shown in Fig. 1a.

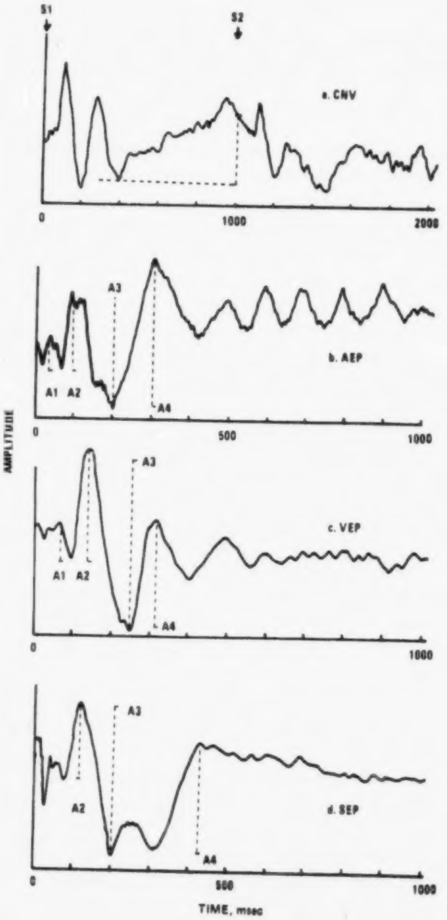

Fig. 1. Measurement procedures for CNV amplitude (a) and peak-to-peak components of auditory (b), visual (c), and somatosensory (d) evoked potentials. CNV amplitude was measured at S2 onset relative to the maximum positive peak 300 to 400 msec after S1 onset. Negativity upwards.

Auditory (A), visual (V), and somatosensory (S) evoked potentials were assessed twice beginning at times 10 and 120 min. Blocks of 100 stimuli in each modality were presented in the order A-V-S. A fixed ISI of 4.17 sec was used in all modalities. AEPs were elicited by 1 msec, 96 dBA clicks. A special preheated fluorescent tube 40 cm in front of the subject's eyes was used for visual stimuli. Intensity was adjusted during a pretest to obtain a clearly defined VEP with eyes closed. SEPs were elicited by dc stimulation of the median nerve of the left arm 10 cm proximal to the wrist. The intensity was adjusted for each subject to obtain a clear sensation just below the pain threshold. A 1-sec sweep rate and N=100 were used for EP summations. Peak-to-peak component measures for each modality are illustrated in Fig. 1b-d.

Heart rate was monitored throughout the experiment. Average heart rate/min was determined during each subtest.

Behavioral measurements included auditory vigilance performance (between 6 and 8.4% COHb), an addition task from the Horn Intelligence Test, and a memory test (10-11% COHb). The memory test consisted of 11 nonsense syllables presented visually and orally, each repeated 10 times for 2.5 sec. Subjects were tested immediately after presentation and 17 min later (Butollo 1969). A subjective mood scale was completed at the beginning and end of the experiment. Nonparametric tests were used to evaluate significance.

Results

Most variables failed to show clear changes in response to CO exposure, although selected measures showed significant effects. No difference in the EEG power spectrum could be demonstrated for COHb levels of about 10%, although a general trend in diminution in power density values was seen at levels of 4% COHb for all frequency bands. During CO exposure, AEPs were slightly reduced in amplitude for components later than 50 msec. No changes in peak latencies could be seen. Amplitude reduction in relation to control was seen during the first measurement (< 4.5% COHb), but not the second (> 8.6% COHb). For some subjects this difference was very clear (Fig. 2), but for the whole group the differences were not significant (Table 1). No changes in amplitude of VEPs attributable to CO were observed. Longer latencies under CO for the late components were more pronounced during the first measurement series (4.9% COHb) than the second (9.1% COHb, Table 1). After median nerve stimulation, amplitude reductions of all late EPs could clearly be seen under CO, but no changes in latencies were observed. The CO effect was more pronounced during the first (5.5% COHb) than the second measurement (9.7% COHb, Table 1).

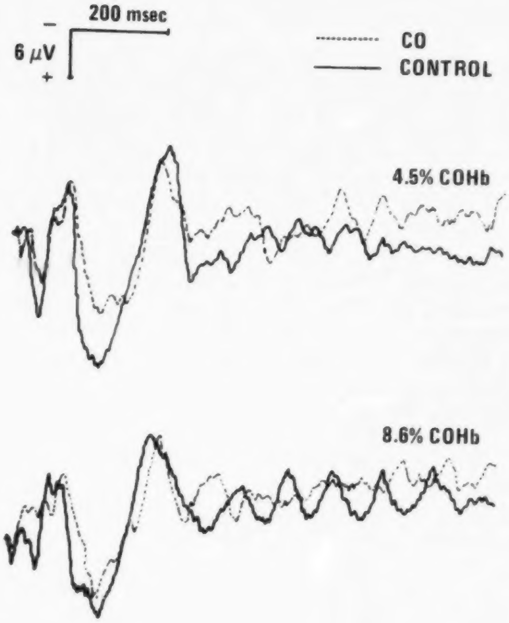

Fig. 2. Example of AEPs recorded in one subject during control and 200 ppm CO conditions at two different points on the COHb uptake curve.

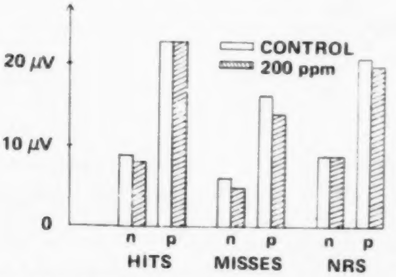

Fig. 3. Mean CNV amplitude for hit, miss, and nonrelevant (NRS) trials of the vigilance test during exposure and control conditions.

CNV amplitude was measured in relation to P330. The only significant difference in CNV amplitude occurred between CO and control conditions for relevant signals that were not correctly detected ("misses"). In other categories of stimuli (hits, nonrelevant pairs), no CO effect was observed on CNV amplitude (Fig. 3). Pulse rates during exposures below 6% COHb showed a slight depression. In contrast, COHb levels greater than 8% showed a relatively higher pulse rate than control (Fig. 4).

No significant difference in missed signals or false alarms in the vigilance task (Table 2), or in the addition test was observed between CO and control conditions. Not quite as many nonsense syllables were recalled in the CO as in the control condition.

Table 1. Peak-to-Peak Amplitudes (μV) of Evoked Potential Components after Auditory, Visual, and Somatosensory Stimulation

	0 ppm			200 ppm			Diff 0-200 ppm	
	Series 1	Series 2	Diff 1-2	Series 1	Series 2	Diff 1-2	Series 1	Series 2
AEP A1	7	4	*	5	4	NS	NS	NS
A2	16	10	*	13	9	*	NS	NS
A3	29	18	*	26	18	*	NS	NS
A4	24	14	*	24	14	*	NS	NS
VEP A1	3	3	NS	3	3	NS	NS	NS
A2	8	7	NS	7	8	NS	NS	NS
A3	13	17	*	13	16	NS	NS	NS
A4	8	12	*	9	11	NS	NS	NS
SEP A2	8	8	NS	5	6	NS	NS	NS
A3	20	22	NS	13	17	NS	*	NS
A4	18	21	NS	11	15	NS	*	*

*$p < .05$ (Wilcoxon-matched-pair signed-rank comparisons); N = 20 for all comparisons. NS—nonsignificant.

There were no significant differences in mood ratings, although subjects tended to feel less exhausted, less overburdened and less tense after CO exposure.

Experiment 2

Method

Ten nonsmoking, unpaid student volunteers (5 male) aged 20 to 25 and having normal EEGs, participated. Subjects were screened for absence of sleep, cardiac, or pulmonary disturbances. The single-blind experiment included three sessions, separated by at least 14 days. The first session was used for adaptation, and the second and third sessions were used for either control (0 ppm CO) or experimental (100 ppm CO) purposes. Subjects slept in an experimental chamber for about 7 hr each night (10 p.m. to 6 a.m.). EEG was continuously recorded during the night from Cz referenced to a mastoid (M1). EOG was also recorded for rejection of eye- movement-artifact trials during offline sleep stage scoring. Sleep stages were determined by visual EEG inspection, on

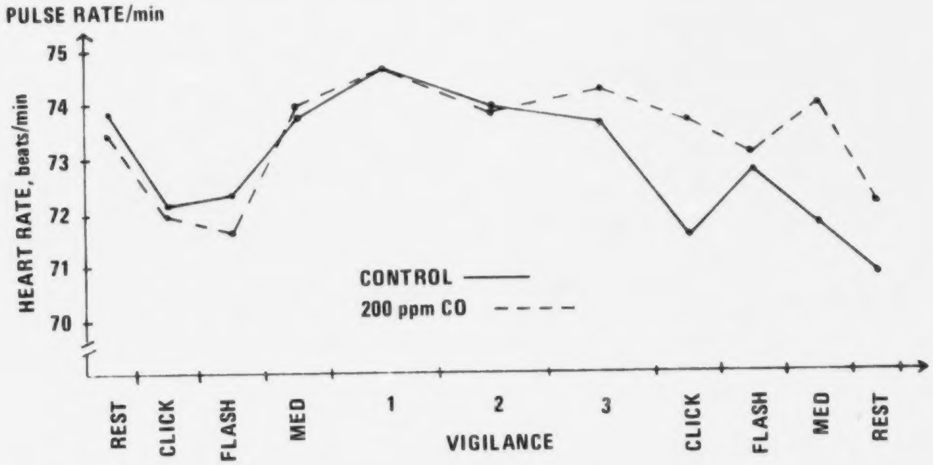

Fig. 4. Average heart rate during successive phases of the experiment.

Table 2. Vigilance Performance

Measurement	Condition	Series (Minutes) 1-20	21-40	41-60	Mean
% Misses	Control	31.4	43.5	55.3	43.4
	200 ppm CO	32.1	48.3	50.9	43.7
% False alarms	Control	7.1	4.9	2.7	4.9
	200 ppm CO	6.7	4.6	4.3	5.2

the basis of 1-min intervals according to Rechtschaffen and Kales (1973) criteria. For EP evaluation, clicks (70 dBA, 3 kHz, 8.9 msec duration) were produced at a random interval averaging 22.6 sec by a loudspeaker placed 50 cm above the subject's head. AEPs were analyzed selectively for different sleep stages. Each AEP was a summation of 30 successive trials. For statistical comparisons of CO and control situations, an average potential was calculated for each sleep stage. Amplitude of negative and positive peaks was measured in relation to a prestimulus baseline. A subjective mood scale was completed before and after each session. Additionally, the memory subtest of the I-S-T intelligence test (Amthauer 1953) was used to assess recall. A 3-min learning period was followed by testing 6 min later and again the following morning. COHb level was calculated by means of the Coburn et al. (1965) formula. Nonparametric tests were used to evaluate the data ($p < .05$).

Results

Exposure to 100 ppm CO during sleep, calculated to raise COHb levels to 10-12%, caused a significant change in sleep-stage distribution. During CO exposure, the percentage of sleep stages 3 and 4 increased, and stage 2 and REM sleep decreased (Table 3). Compared to the control condition, REM sleep decreased by 18% and deep sleep (stages 3 and 4) increased by about 29%.

AEP latencies analyzed during sleep stage 2 showed no differences between control and CO conditions (Table 4). All positive components clearly increased during CO exposure. The P200 difference was significant, while the P900 and P2000 differences fell just short of significance. Negative components did not differ between control and CO conditions. The amplitude change observed during sleep stage 3 resulted exclusively from enhancement of the positive peaks.

In sleep stage 4 (Table 4), the peak latency of the P200 component was significantly lengthened during CO exposure. Amplitude measures also showed very clear changes (Fig. 5, Table 4). All positive components were significantly larger under CO, and negative components showed a nonsignificant decrease in comparison to the control condition. While the AEP of sleep stage 4 showed no change in absolute size due to CO, there was a significant shift of the whole waveform in the positive direction.

Significantly more words from the memory test were remembered after the control night than the experimental night. No significant differences were found on the subjective mood scale, but there was a tendency towards negative responses in the CO condition. Similar results have been reported by Bender (1971).

Discussion

The results indicate that the SEP is the most sensitive to CO influence of the EPs examined. Reductions of all late SEP components under CO were clearly apparent (Table 1). That all sense modality

Table 3. Percent Time in Each Sleep Stage

Condition	Awake	Stage 1	Stage 2	Stage 3 + 4	REM
Control	12.2	6.3	58.5	10.4	12.6
100 ppm CO	13.0	5.5	57.8	13.4[a]	10.3[a]

[a] $p < .05$, Wilcoxon matched-pair signed-ranks comparisons vs. control values

Table 4. Latencies (L) and Amplitudes (A) of AEP during Different Sleep Stages

Sleep Stage	Measurement	Condition	P1	N1	P2	N2	P3
2	L,msec	Control	206	330	424	602	1024
		100 ppm CO	206	335	412	577	1017
	A, μV	Control	+15	−16	−2	−29	+24
		100 ppm CO	+19[a]	−18	−5	−37	+31
3	L,msec	Control	198	418	922	1572	2036
		100 ppm CO	204	441	919	1600	2152
	A, μV	Control	+10	−43	+28	−20	+7
		100 ppm CO	+15[a]	−41	+34	−20	+13
4	L,msec	Control	186	445	963	1493	2038
		100 ppm CO	209[a]	464	920	1524	1986
	A, μV	Control	+4	−43	+30	−21	+1
		100 ppm CO	+13[a]	−29	+37[a]	−19	+10[a]

[a] $p < .05$ (compared to control value); Wilcoxon; N = 10.

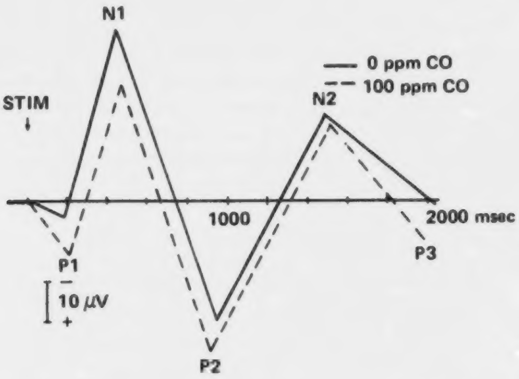

Fig. 5. Effect of CO exposure on the auditory evoked potential during stage 4 sleep.

decrements in amplitude or changes in latency were greater at lower (4.5 to 5.5%) than at higher (8.5 to 9.7%) COHb levels is noteworthy. Winneke et al. (this volume) examined AEPs in a CO study using a vigilance task with two levels of monotony. The authors summarize their results by stating that no obvious effects due to CO or to monotony were apparent. However, analysis was done separately for negative and positive peaks and examination of peak-to-peak amplitudes suggests that a reduction in mean amplitude occurred in the monotonous condition. Reductions of 13, 14, and 23% were seen at COHb levels of 6.5, 7.4, and 11.3%, respectively.

Since conscious mediation of cortical function is suspended during sleep, impairments in CNS function due to exogenous or endogenous factors may be observed more clearly. Colmant (1972) found a CO-induced decrease in REM sleep in animals and O'Donnell et al. (1971a) reported trends toward alterations in human sleep patterns. The data reported here revealed a significant alteration of sleep patterns under CO. All EP components in sleep stage 4 were significantly enhanced, whereas in sleep stage 2, only P100 was significantly larger in amplitude. Subjects appear more susceptible to CO effects in deep sleep than in shallow sleep. The positive translocation under CO should be considered in relation to general dc shifts, facilitation, and the availability of neurons during different sleep-stage arousal levels.

EP methods can demonstrate CO-induced changes of CNS functioning at low COHb levels when compensating mechanisms are not in effect and at high COHb levels when compensating mechanisms are insufficient. During sleep stage 4, EP component amplitudes were significantly augmented, but no differences in AEP amplitudes were found in subjects aroused after 7 hr sleep exposure to 100 ppm CO. One may hypothesize that awakening activated a compensatory mechanism absent during sleep.

No significant impairment of vigilance performance was observed during CO exposure. Winneke et al. (this volume) reported similar results. Groll-Knapp et al. (1972) found a significant decrement in vigilance performance during CO exposure (50, 100, 150 ppm) for 2 hr. Failure to replicate these results may be due to variations in experimental design. Heart rate was higher during CO exposure than the control condition, and one could infer that the increased rate resulted from compensation for the additional CO burden.

During the acoustic vigilance task, CNV measurements were obtained, but CNV differences were observed during CO and control conditions only when trials were selectively averaged for "hits" and "misses." Groll-Knapp et al. (1972) reported a significant decrease in CNV amplitude as the level of CO exposure increased. Failure to replicate these results may again be due to alterations in design or other uncontrolled variables.

CO effect on subjective feelings was different after short-term and sleep exposure. Following short-term exposure, subjects felt less exhausted, less overburdened, and less tense than after the control condition, although these changes were not significant. Weber et al. (1975) reported similar, but significant, results. After sleep exposure, however, subjects felt more negative.

Different studies of behavioral and neurophysiological parameters under moderate CO exposure have shown contradictory results. Neurophysiological measures appear to be more sensitive than behavioral measures to the effects of low COHb concentrations. These effects are more consistent during sleep exposure when the inter- and intraindividual variability is lower. One reason that effects are difficult to replicate in awake subjects may be that healthy young adults are able to mobilize compensatory mechanisms during short-term exposure. Differences between experiments using low-level CO exposures could result from a disassociation between the onset of CO-induced changes in CNS function and the onset of compensatory mechanisms.

Conclusions

The public is exposed to environmental toxicants without choice, knowledge, or defense. Healthy persons as well as others with increased risk due to functional disturbances or disease are exposed indiscriminantly. The adverse effects of simultaneous exposure to multiple environmental stressors, moreover, may be synergistic. Results of the present experiments suggest (1) that appropriate neurophysiological measures reflect functional changes during moderate CO exposure; (2) that measures of CNS function should be included in standard test batteries used to assess the adverse effects of environmental substances; and (3) that neurophysiological evidence of this type should be considered in establishing exposure standards. Sleep studies may be helpful in avoiding certain theoretical and practical problems in the study of influences of environmental factors on physiological and neurophysiological mechanisms.

APPLICATION OF ERP TECHNIQUES IN NOISE RESEARCH

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Unlike other agents in clinical toxicology that are subject to neurobehavioral research techniques, noise is not a toxicant that produces central nervous system (CNS) poisoning, and there is no conclusive evidence that it has any effect on health other than the loss of hearing that may result from prolonged exposure. However, few would deny that noise is an environmental insult simply because of its psychological effects; and since it may be important to determine how far other agents have specific effects that may be differentiated from general reactions such as distraction, irritation, or fatigue, noise is certainly among the problems that should be considered in stress research.

The potential contribution of ERP techniques to noise research may best be examined by reviewing what behavioral research has, and has not, already achieved. A striking feature of research in this field is that psychologists have had great difficulty in demonstrating any noise effects of practical importance, and those they have found have proved in some ways rather puzzling (Broadbent 1957, 1971). Noise can be a nuisance and the reasons why hardly seem mysterious. Noise distracts us, and may alarm or startle us as well. So where is the problem?

Investigations of distraction have tested performance on a wide variety of tasks, ranging from simple reaction time (RT) to complex intellectual skills, under the most distracting noises imaginable. The uniform finding has been a transitory disturbance of performance when the noise is turned on and another when it is turned off, the amount of disturbance being roughly proportional to the change in noise level, up or down (Teichner 1963). These features are reminiscent of an orienting response, in which case habituation would be expected, and it is indeed found that after the initial disturbance the subject continues with his performance apparently unimpaired.

"Apparently" is used advisedly. Persistent distracton effects can be found if performance is closely examined. Fisher (1972), using a choice reaction task with bursts of noise at random intervals, found that response was slowed – but only on those trials where the noise occurred less than 200 msec before response. It appeared to affect response initiation, as if deciding to ignore the noise interfered with deciding which response to make. This suggests that distraction effects may be so subtle that they will not be detected by gross average measures but only by such microanalysis, or by increasing the sensitivity of performance measurement in some other way (Poulton 1965). Such an approach runs the risk of obtaining effects that are of theoretical interest but little practical importance (Chapanis 1967). Common observation indicates that people can perform many tasks surprisingly well in noise. Nevertheless, they are apt to complain of the strain it places upon them, and this complaint is supported by evidence of increased muscle tension and elevated heart rate (Davies 1968).

The possibility that environmental stressors may have effects that are not apparent in performance is a major reason for considering whether ERPs may provide more sensitive measures. In the case of distraction, there is an obvious lead: in his review of psychological research on the CNV, Tecce (1972) remarks that "distraction is one of the most powerful variables that can disrupt CNV development." Pioneer investigations at the Burden Institute (Dargent and Dongier 1969) showed that the CNV was diminished by distractions, such as conversation or music, that continued throughout the trial. The effect seemed to be most marked on the "early CNV," and to depend on how effective the distraction was for the individual subject. A series of experiments by Tecce and his collaborators (1972, and this volume) have attempted to ensure the effectiveness of distraction by using a secondary task. Again it was mainly the early CNV that decremented, and RT increased as well.

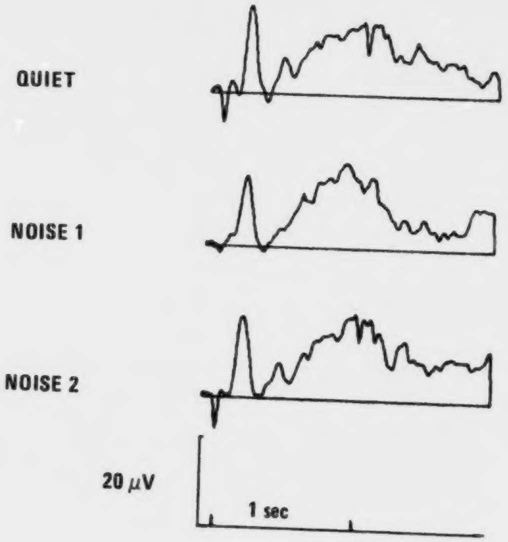

Fig. 1. CNVs from three sets of eight consecutive trials, one set performed in quiet followed by two in continuous white noise at 100 dB.

None of these investigations involved what is normally referred to as noise. The present writer therefore carried out some informal observations, using a paradigm in which both S1 and S2 were visual. Continuous white noise at 100 dB produced a slight effect on the early CNV on the first few trials; but averaged over the first set of eight, it was barely perceptible, and the effect was not apparent on the second set (Fig. 1). RT was, if anything, a little faster, with some tendency toward premature response.

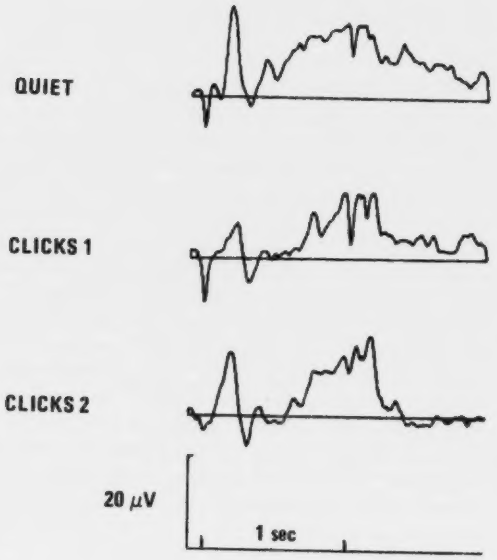

Fig. 2. CNVs from three sets of eight consecutive trials, one set performed in quiet followed by two with loud clicks presented at short random intervals.

This result is perhaps not surprising. Compared with conversation, white noise is meaningless and, by definition, featureless. It is difficult, therefore, to see white noise as distracting. Loud clicks and tones, presented at irregular intervals, certainly sound more distracting. Clicks clearly depress the early CNV during the first eight trials, but there is substantial recovery on the second set of trials (Fig. 2). Even loud tones are soon gated out.

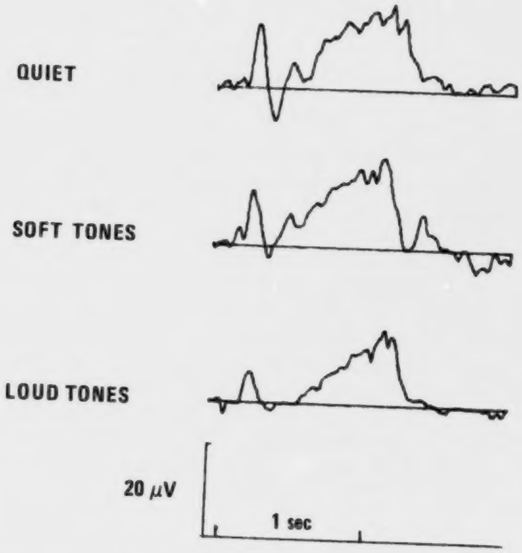

Fig. 3. CNVs from three sets of eight consecutive trials, one performed in quiet, one with an unpredictable series of soft (60-dB) tones preceding S1, and one with a similar series of loud (100-dB) tones.

All these effects come from stimulation that continues throughout the trial. What happens with more localized stimuli? Tecce (1972) reports that distraction after S1 also decreases CNV and increases RT. Distraction before S1 decreases CNV, but RT is not affected. McCallum and Walter (1968) report little effect on CNV when the distractor is in a different modality from S1. My observations suggest that intensity is important, since compared with soft tones, loud tones have a marked effect across modalities (Fig. 3). Since the early CNV again seemed to be affected, the foreperiod was increased to 3 sec. (Fig. 4). The whole CNV appeared to be flattened, except for a very local readiness potential. RT was unaffected.

Summarizing, stimulation presented throughout the trial, or during the foreperiod, or before the warning signal, all depress the CNV, especially the early CNV; but the effect is transitory, and RT is affected only when distraction is present during the foreperiod. Stimulation before S1 does not affect RT, even though flattening of the early CNV suggests that the alerting effect of the warning signal has been largely eliminated. The explanation is not clear. Tecce (1972) pointed out that speech (or any continuous stimulus) causes a baseline shift. Does this mean that the alerting effect of the warning signal has been preempted? Or are these ERP effects epiphenomena without functional significance?

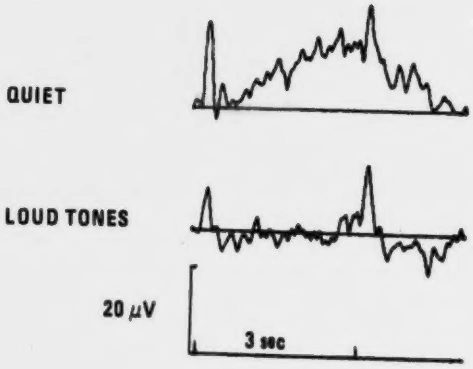

Fig. 4. CNVs from two sets of eight consecutive trials, one performed in quiet, the other with an unpredictable series of loud (100-dB) tones preceding S1. The foreperiod has been lengthened to 3 sec.

The relevance of this question to the present discussion lies in the apparent dissociation of ERP and behavioral effects. The effect on RT seems to be localized; distraction must occur close in time to the response (Fisher 1972). The ERP effect seems much less localized; loud stimuli before S1 have an effect lasting several seconds. Can this be a case of an ERP providing a more sensitive measure than behavior? This seems arguable. There would be no difficulty if stimulation before S1 had a greater effect on the ERP with increasing intensity (which seems to be true) *and* only began to affect RT at high intensity; but the limited observations presented here suggest that it does not affect RT at all.

This result raises two issues. First: to use an ERP effect as an index of environmental insult requires validation against some practical criterion, such as disease, discomfort, or inefficiency; so what constitutes practical validation? Second: it is not enough to get an effect; it is equally important, for practical as well as theoretical reasons, to know what kind of effect it is. Tecce (1972) proposed that to demonstrate distraction, it is necessary to show both that the alleged distractor is actually processed, and that there is performance decrement on the central task. According to this criterion, the effect of stimulation before S1 cannot be described as distraction. The interpretation of dual task performance itself poses problems that should not be underestimated (Brown 1964, Rolfe 1969). It seems clear that the nature of effects obtained with the CNV requires further investigation.

The problem of identifying distraction can be illustrated further by turning to the one case where noise has been shown to have more than a transitory effect. Persistent noise effects have been shown on so-called "continuous performance tasks," such as vigilance, serial reaction, and tracking (Broadbent 1971). The main feature of these tasks seems to be that it is difficult to compensate for failing performance by increasing effort. Compensatory effort is so endemic a problem in stress research that we should seriously consider whether ERP techniques could provide an indicator of such effort.

The effect of noise on continuous performance tasks was initially attributed to distraction (Broadbent 1953). It was argued that as subjects continued to work at extremely boring tasks, their attention tended to wander, and was increasingly likely to be captured by noise. The effect on performance might well be described as a lapse of attention; but there was never any direct evidence that attention was captured by noise, and there are a number of reasons why this seems implausible. As noted above, it is not clear how continuous broadband noise, commonly used in these experiments, can be described as distracting. This doubt was reinforced when it was discovered that tasks sensitive to noise were also sensitive to a wide range of other stressors, including some, such as sleep deprivation, that are even more difficult to see as distracting. This raised the question whether different stressors affected the tasks in the same way; and this question was answered by investigating the interaction of stressors.

Interaction effects are of considerable practical importance. Stressors that have little effect in isolation may have marked effects in combination (Chapanis 1967). Noisy environments commonly contain other stressors – one reason why it has been difficult to determine whether noise exposure is implicated in circulatory disease (Broadbent 1961). Interactions are also important theoretically, as a way of determining whether stressors affect the same or different mechanisms. If different mechanisms, their effects should be independent and additive; if the same, they should interact.

Experiments on combinations of stresses (Wilkinson 1969) have shown that noise is antagonistic to sleep deprivation but synergistic with incentive, thus placing it on a continuum from drowsy, slow but accurate performance to over-excited, fast but erratic performance – a dimension that has been identified as "arousal." The arousal theory of stress (Broadbent 1971) supposes that arousal is related to performance by an inverted-U function. The main effect of arousal is upon selective attention of the "stimulus set" or filtering" type, which operates upon the intake of sensory information. In states of high arousal, attention becomes selective to the point of "tunnel vision," when performance deteriorates because there is insufficient sampling of low probability sources. Conversely, low arousal reduces the bias towards the probable, attention is insufficiently selective, and performance deteriorates because there is insufficient sampling of task stimuli (Hockey 1973).

This leads to a predicted ERP effect, since Picton and Hillyard (1974; see also Tueting, this volume) have argued plausibly that filtering is reflected in the amplitude of the N1 component of the auditory evoked potential and analogous components in other modalities. These ERPs are supposed to reflect the activation of a mechanism that selectively passes sensory information for further processing on the basis of primitive feature analysis, and in accordance with attentional demands that have usually been set by instruction. Loveless (1977) presents evidence that when subjects anticipate noisebursts loud enough to be disturbing, attention is biased away from a visual task, and that the behavioral decrement is accompanied by enhancement of the N120 component of the visual evoked response to the imperative stimulus.

A similar effect should be obtained when a continuous performance task is performed in the presence of intense broadband noise, which is believed to heighten arousal, since N1 is increased by incentive and decreased in drowsiness. Otto and Benignus (this volume) report the novel finding that when performing a similar task in low-frequency noise, subjects complain of drowsiness rather than irritation. There is an increase in the number of missed signals, which with a constant false-alarm rate would indicate a decrement in the d' parameter of signal detection theory, which is the result obtained under sleep deprivation (Wilkinson 1969). While their ERP measurements do not entirely dissociate evoked response components from slow potentials, they strongly suggest that the amplitude of the N110 component of the visual evoked response decreases. The data therefore consistently indicate a decrease in selectivity with lowered arousal. It is not clear, however, *why* low-frequency noise should have this effect.

The point here is that arousal theory specifies only the relationship between arousal level and performance; the relationship between stressor level and arousal level remains to be determined, and experience with a number of stressors suggests that it is unlikely to be simple. A good example is the case of thermal stress, which also illustrates more generally the problems that arise in applied research when investigators aim directly at practical results with little concern for theory (cf. review by Griffiths 1970). Much early effort attempted to link subjective comfort directly with environmental variables, resulting in a number of stress indices, such as the effective temperature scale, none of which is really satisfactory. Attempts were then made to relate performance to effective temperature. This led to a mass of inconclusive and inconsistent results, which left it unclear even what kind of tasks were affected by thermal stress, let alone why or how.

It was then suggested that performance might be related to body temperature rather than ambient temperature, but this approach was not entirely successful either. A particularly puzzling feature was the temporal pattern of performance: there seemed to be an initial disturbance, followed by recovery, but sometimes there was a later deterioration. The explanation appears to be that the initial impact of heat raises the level of arousal, but arousal subsides as soon as the disturbance of thermostasis is countered by physiological compensation. As long as the compensatory reaction is succeeding, arousal remains normal; but if compensation shows signs of failing, arousal rises again. The critical variable is neither skin temperature nor core temperature, but the relationship between them; performance deteriorates when this relationship changes in such a way as to threaten a displacement of core temperature. The same relationship appears to underlie subjective discomfort (Provins et al. 1973). Thus, with an adequate account of the stress reaction, physiological, performance, and subjective effects all fall into place. This seems to be a crucial issue in stress research. In the case of hypoxia it may be equally important to understand the compensatory mechanisms and the factors that control their threshold.

It may be precisely because such an analysis has been lacking that the psychological effects of noise stress have been puzzling. It has never been clear why effects have been found only at intensities above 90 dB; and again the temporal pattern has been odd. The effects do not appear until the subject has been working in noise for at least 15 min, and when the noise is turned off, performance in quiet continues to suffer for about the same length of time (Hartley 1973). A time-lag of this order strongly suggests a humoral mechanism, and recent evidence (Simpson et al. 1974) strongly implicates blood-sugar level. This idea, of course, is not new – Selye (1950) saw it as part of his "general alarm reaction" – but the precise details are important. It appears that an initial neural response, sustained by the secretion of glucagon and epinephrine, produces a peak in blood-sugar in about

10 min. If the stress is not too severe, this is countered by the release of insulin (to prevent loss of glycogen from the muscles) so that the trend is reversed towards hypoglycemia. This time-course correlates very well with the performance change, and the relationship appears to be causal because the effect can be prevented by preloading with glucose.

If the reaction to intense noise is viewed as part of a general stress response, it may be easier to formulate a comprehensive view of noise effects. The discovery of the persistent effect of continuous noise has tended to divert attention from intermittent noise, which is perhaps more common in practice. While sounds of moderate intensity tend to produce only a transient disturbance, a series of experiments by Woodhead (see Broadbent 1971) has shown that intense bursts of noise produce a more prolonged and persistent effect that seems to involve an impairment of sensory intake. It can hardly be coincidence that the threshold for this effect, like that of continuous noise, is in the region of 90 dB, nor that it is at about this level that the defence reaction replaces the orienting reaction.

Attempting to interpret the distraction and stress effects of noise in terms of orienting and defence reactions is not just a translation into jargon; it allows us to draw upon what is known about these responses. For example, there should be differences in threshold between meaningful and meaningless noises, because Sokolov (1963) has shown that when a sound has signal value, it elicits the orienting reaction over a wider range of intensities. Distraction may be produced by meaningful stimuli near auditory threshold, and a sound that may be stressful when task-irrelevant may be acceptable as a signal. Stimuli that are biologically important, either because of intensity or because of acquired significance, do not habituate readily. This is of practical importance because it has proved difficult to recommend a critical level for intermittent noise precisely because of uncertainty about habituation.

An adequate account of noise should also comprehend subjective reactions. Psychologists have shown some tendency to shy away from the problem of annoyance, perhaps sharing the view of Broadbent (1957) that it is "largely unpredictable by scientific methods." While some people are more sensitive to noise than others, and annoyance is to some extent idiosyncratic, treating it as strictly subjective provides an easy escape for noise makers, and perhaps diverts scientists from problems that merit study. The minimal condition for annoyance seems to be distraction, in that it is precisely the "attention-getting" features of sounds that are universally found to be annoying. These features correspond strikingly with standard determinants of the orienting reaction, such as intensity, novelty, uncertainty, and complexity. These are also features that have linked with late components of the auditory evoked potential. N1, for example, though clearly related to physical features such as intensity, is not simply related to them. It reflects change in intensity, unexpectedness, and the extent to which a stimulus demands further evaluation of its significance and so diverts processing capacity from current activity. If annoyance is subjective in the sense that some people are more sensitive than others, the same has been found in evoked potentials – for example, Buchsbaum and Silverman (1968) report that N1 amplitude varies along the personality dimension of augmenting-reducing – and the idiosyncratic aspect of annoyance seems to relate to the acquired significance of sounds, which may be reflected in the evoked potential. In short, ERPs might serve as indices of noisiness that would be less open to attack as being subjective in the pejorative sense. Insofar as there is reason to distinguish orienting, defense, and startle reactions to noise, more sophisticated multidimensional measures of subjective response need to be developed.

In applying ERP techniques to noise research, it may be useful to recognize that there are two relatively distinct arousal systems, and that the phasic defense reaction may be sustained by a humoral mechanism. A number of ERPs have been tentatively linked with the orienting reaction (Klinke et al. 1968; Tueting, this volume; Loveless 1976), but there has been little attempt to work out a model of its mechanisms and the relation of ERPs to its presumed function of increasing perceptual sensitivity (Loveless 1975). A few attempts have been made to relate ERPs with traditional autonomic measures of orienting (Roth et al., this volume), but unfortunately not those such as the forehead vasomotor response or heart rate (Graham and Slaby 1973) that differentiate the orienting and defense reactions.

Furthermore, there has been no exploration of relationships with EEG desynchronisation. For instance, the effect of hyperventilation on the EEG is potentiated by hypoglycemia, a fact which may be relevant when considering possible similarities between noise and hypoxia. Although this relationship between the EEG and brain metabolism is well-known, very little is yet known about the relationship between either and ERPs.

This review has emphasized the critical importance of theory in dealing with practical issues. Among the many difficulties in applying laboratory research to practical situations is what Chapanis (1967) calls "variable naming." It is tempting to apply the results from a continuous performance test to some real-life task, such as industrial inspection, on the grounds that both involve "vigilance." Clearly, this sort of extrapolation is justified only to the extent that the two tasks do in fact involve the same functions, which is by no means guaranteed by the naming. This consideration is particularly important in stress research, because researchers have tended to limit themselves to a handful of stress-sensitive tasks. There is an obvious strategic advantage in doing so, but it then becomes very difficult to apply the results to a wide variety of real-life situations. We do not have an adequate taxonomy of tasks (Wilkinson 1969), and it is difficult to see how one will be achieved without analyzing tasks into component functions. The usefulness of ERP techniques in meeting this theoretical challenge might be their most important contribution to stress research.

LOW-FREQUENCY NOISE, SELECTIVE ATTENTION, AND EVENT-RELATED POTENTIALS

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Low-frequency noise (LFN) generated by major appliances such as heating and refrigeration equipment is a pervasive component of domestic and industrial environments, but little is known about the effect of LFN on the central nervous system. Noises below 100 Hz are seldom perceived as irritating, although people sometimes complain that the continuous "hum" of motors makes them drowsy. This study explored the neurobehavioral effects of LFN in the 11.5- to 350-Hz range. Methods and behavioral results have been detailed elsewhere (Benignus et al. 1975). This paper describes the analysis of vertex event-related potentials (ERPs).

Methods

Twenty-seven male subjects aged 18 to 31 were paid to perform a 2.5-hour numeric monitoring task in an acoustic chamber. Single-digit numerals were displayed for 0.05 sec at the rate of 1/sec using a light-emitting diode. Subjects viewed nine pseudorandom series of digits, with instructions to press a hand switch whenever three consecutive even or odd numbers appeared. One-digit, two-digit, and three-digit sequences were equiprobable. Each series lasted 12.5 min and contained approximately 111 target sequences.

The output of a random-noise generator was filtered to obtain an upper band of 91 to 350 Hz and a lower band of 11.5 to 44 Hz. Noise was radiated free-field at a moderate sound-pressure level of 80 dB during series 2,4,6, and 8. No noise was radiated during series 1,3,5,7, and 9.

EOG and vertex EEG referred to linked ears were recorded using amplifiers with 2.2-sec time constants. Signal averages were computed separately for hit (H), correct rejection (CR), and miss (M) trials using a PDP-12 computer. Trials containing EOG artifact were rejected from averages. ERP data from six subjects were not analyzed because of excessive eye movements.

ERP measurements are illustrated in Fig. 1. CNV was measured as the mean amplitude of a 128-msec epoch preceding S3 relative to a 128-msec baseline preceding S2. The maximum negative and positive peaks following S3 were measured relative to the same baseline. The mean latencies of these peaks, averaged across subjects and conditions, were 110 msec (N110) and 456 msec (P456), respectively, relative to S3 onset. In order to minimize the possibility that N110 measures were confounded by the slow negative shift preceding S3, CNV values were subtracted from N110 values prior to statistical testing.

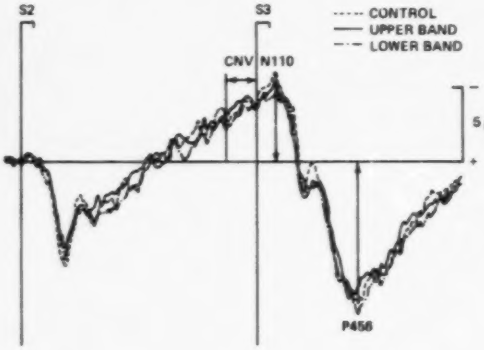

Fig. 1. Summary averages of hit trials during control, upper-, and lower-noise band conditions for 17 subjects. Time base: 1 sec from S2 onset to S3 onset.

Vertex ERPs were averaged selectively for H, CR, and M trials. Twenty-one subjects were used in the CR analysis. Four low-performance subjects were excluded from the H analysis due to insufficient hits in some conditions. Only seven subjects missed enough trials for inclusion in the M analysis.

Results

Subjects missed more target strings during noise than control conditions, although M rates did not differ significantly between the two noise conditions. Table 1 shows the average number of misses for noise and control series of high-, medium- and low-performance subjects. False alarm rates were uniformly low in all conditions.

Table 1. Average Number of Misses during Control and Noise Series

Performance level	Average misses/series	
	Control	Noise[a]
High (N=7)	2.2	3.0
Medium (N=7)	7.0	8.4
Low (N=7)	26.9	38.8
± 1.96 x S.E.[b]	± 2.69	± 4.68

[a] Upper and lower bands combined.

[b] 95% confidence interval = mean ± 1.96 x standard error of mean.

Fig. 1 depicts the summary averages of H trials during control, upper-, and lower-band noise conditions for 17 subjects. The subtle effects of noise exposure on ERP amplitudes are shown in Table 2. Control means were subtracted from upper and lower band means for each subject in order to reduce the dimensionality of the data for statistical testing. The null hypothesis of no noise effect was rejected by means of a single-factor multivariate test [$F(6,11) = 6.40$, $p < .004$]. Univariate tests indicated that N110 amplitude decreased during upper- [$F(1,16) = 10.93$, $p < .004$] and lower-band noise [$F(1,16) = 4.35$, $p < .053$], CNV decreased during lower-band noise only [$F(1,16) = 8.53$, $p < .01$], and P456 amplitude was not affected by LFN.

None of the ERP amplitude measures discriminated between noise and control conditions in CR trials. No behavioral criterion was available, however, to indicate whether or not subjects were attending to stimuli during CR trials (i.e., subjects were not required to respond following two-digit strings). Selective averages of CR and M trials in seven subjects (Fig. 2) illustrate the problem of interpreting CR averages without a behavioral criterion. Note the attenuation of CNV and N110 and the absence of P456 in the M average. The extent to which CR averages included and were distorted by M trials could not be determined.

Latencies of the largest positive component following each stimulus in CR trials were also measured. Latencies increased successively following S1 (155.9 ± 37.4 msec), S2 (184.1 ± 46.1), and S3 (455.6 ± 99.6). The 28-msec difference between S1 and S2 was significant (Wilcoxon: $T=10$, $N=21$, $p < .01$). The discontinuity between S2 and S3, however, suggests that P184 and P456 do not represent the same neuroelectric process. Fig. 2 illustrates this point. Two distinct positive components are evident following S3 in the CR average. The earlier peak corresponds to the positive component following S1 and S2. As noted above, the second positive component (P456) is absent in M trials.

Table 2. Hit Trials: ERP Amplitude (μV) as a Function of Noise Exposure

Noise exposure	CNV	N110	P456
Control	-3.9	-5.7	13.1
Upper band	-3.8	-4.7[a]	12.0
Lower band	-3.1[a]	-4.4[a]	12.7

[a] Significantly different from control values as determined by *post-hoc* univariate tests (see text).

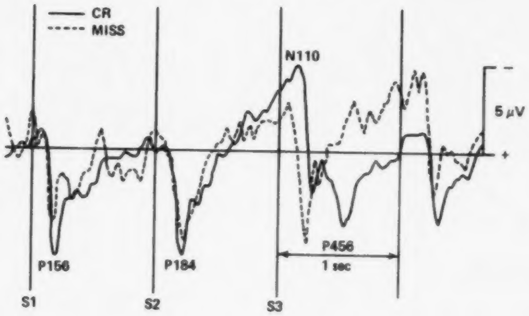

Fig. 2. Summary averages of miss trials superimposed on correct rejection (CR) trials of seven low-performance subjects. The P456 component following S3 in hit and CR trials was absent in miss trials.

Discussion

Slight, but significant, decrements in vigilance performance and N110 amplitude were observed during exposure to low-frequency continuous noise of moderate intensity. The experimental situation may be compared to the monotony and social isolation of an individual driving a long distance. Engine hum, tires, and air-conditioning could generate noise of comparable frequency and intensity. The potential deleterious consequence of impaired vigilance during driving is obvious.

Do the convergent decrements in behavioral and ERP measures reflect an impairment in selective or general attention? Available evidence does not support a general attentional hypothesis. (1) A parallel change in P456 amplitude would be expected if the effect were nonspecific. (2) There is no evidence that components analagous to N110 vary as a function of arousal level. For instance, Picton et al. (1974) did not observe any change in auditory components earlier than 250 msec during the transition from waking to sleep. (3) If LFN induced drowsiness, a decrease in beta and alpha frequencies accompanied by an increase in theta and delta frequencies would be expected. No noise-related changes in EEG spectra were observed (Benignus et al., in preparation).

An alternative hypothesis is that selective attention, rather than general arousal, was impaired by LFN. That is, noise may have interfered with the ability of subjects to "tune in" or concentrate on the numeric display. Schwent and Hillyard (1975) provide evidence that the auditory N1 component, analagous to N110, reflects selective attentional processes. They observed an 82% intramodal enhancement of N1 in *attend* compared to *ignore* conditions of a complex pitch discrimination-spatial localization task. Related findings have also been reported in visual and somatic modalities (Schecter and Buchsbaum 1973, Velasco et al. 1973).

The latency difference between the prominent positive component following the first and second digits is worthy of comment. This difference was not associated with any change in amplitude. Presumably S1 provided little information, while S2 alerted subjects to prepare for possible response. Thus, the amount of information conveyed by the stimulus appears to have been encoded in the latency rather than the amplitude parameter. This evidence suggests that latency and amplitude parameters may reflect orthogonal dimensions of information processing. Friedman et al. (1975) have reported similar findings in a linguistic task. The present paradigm could provide a useful vehicle to further elaborate the functional significance of the expanding family of late positive ERP components.

In conclusion, LFN of moderate intensity was found to impair performance of a numeric-monitoring task and to reduce the amplitude of a negative evoked potential component peaking at 110 msec. Results suggest that LFN interferes with selective attention rather than general arousal.

PARADOXICAL EFFECTS OF CARBON MONOXIDE ON VIGILANCE PERFORMANCE AND EVENT-RELATED POTENTIALS

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Behavioral impairments have been observed in several vigilance experiments during low-level carbon monoxide exposure (Beard and Grandstaff 1975, Fodor and Winneke 1972, Groll-Knapp et al. 1972, Horvath et al. 1971). Two recent negative reports, however, demand a cautious reappraisal of the relationship between CO exposure and vigilance performance. Groll-Knapp et al. (this section) failed to find any CO-related decrement in a complex visual vigilance task, and Winneke et al. (this section) were unable to replicate the results of Horvath et al. (1971).

The present experiments were designed to study the effect of 0, 100, and 200 ppm CO on vigilance and event-related potentials (ERPs). A continuous performance task that is sensitive to psychoactive drug effects (Mirsky and Rosvold 1960) and environmental stress (Benignus et al. 1975) was chosen. McCallum (1976) has also demonstrated the usefulness of this paradigm in assessing ERPs.

Experiment I

Methods I

Twenty-eight male volunteers (18 to 35 yr old) were paid $5/hr to participate. Subjects were screened by MMPI, Duke Medical Inventory, and physical examinations to obtain a normal, healthy, nonsmoker sample.

Subjects were exposed double-blind to 0 (N=8), 100 (N=10), or 200 (N=10) ppm CO for 2 hr in a small dimly lit booth (1.7 x 1.7 x 2.0 m), ventilated at 100 ft^3/min. CO concentration was continuously monitored with a Beckman Infrared Analyzer. Blood samples were taken before and after exposure. Carboxyhemoglobin (COHb) levels were determined by the Radford spectrophotometric method (Small et al. 1971). Mean pre/post COHb levels were 0.06/0.12, 0.36/4.64, and 0.41/11.99% for 0, 100, and 200 ppm groups, respectively.

EOG and EEG referred to linked ears were recorded at Cz, P3 and P4 by means of amplifiers with 8-sec time constants. Analog data were recorded on magnetic tape and computer-averaged off-line. Trials containing EOG artifact or blocking were automatically rejected.

Stimuli consisted of single-digit numerals displayed on a light-emitting diode for 0.05 sec at 1.5-sec intervals. Subjects viewed six pseudorandom series of digits with instructions to press a button whenever three consecutive even or odd digits appeared. Each run of 667 stimuli contained 27 target strings. Rest breaks (3.3 min) alternated with monitoring periods (16.7 min) during the 2-hr test.

Results I

Percent misses across runs are shown in Fig. 1. The 100-ppm group missed slightly fewer targets than the control or 200-ppm groups, although group

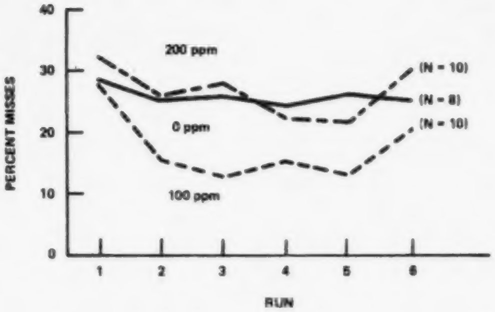

Fig. 1. Percent misses across time as a function of CO exposure level during Experiment I.

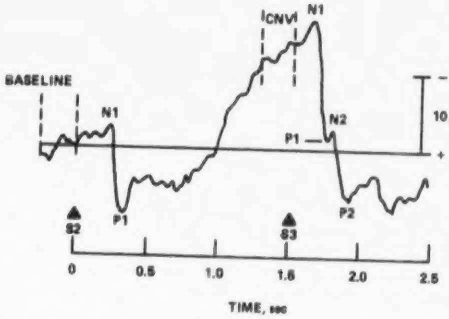

Fig. 2. ERP measurements included CNV amplitude relative to pre-S2 baseline and three peak-to-peak measures: N1P1 following S2 and S3 and N2P2.

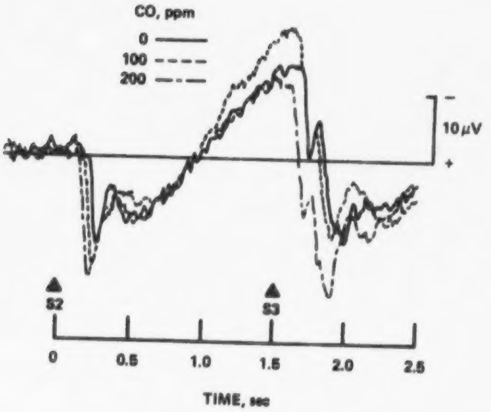

Fig. 3. Summary ERP averages of runs 2 to 6 from 0-, 100-, and 200-ppm CO subjects.

differences were not significant. No vigilance decrement was apparent across time.

Vertex averages digitized at 128 Hz were constructed for target strings, including both hit and miss trials. Four ERP measures were made as shown in Fig. 2. Four subjects were rejected because of excessive eye movement. Two additional subjects who failed to show any consistent CNV were eliminated from the analysis. Run 1 was considered a training run. Measurements were averaged across runs 2 to 6.

ERP results are summarized in Table 1. The effects of CO exposure on CNV amplitude were marginal, with a small increase in the 100-ppm group and a small decrease in the 200-ppm group relative to control subjects. Summary averages of runs 2 to 6 for subjects in the three groups are shown in Fig. 3. CNV amplitude was significantly larger for the 100-ppm than 200-ppm group, but neither exposure group differed significantly from controls.

N1P1 amplitude increased with CO exposure following S2 and S3, although the effect was significant following S3 only. Subsequent analysis, using the CNV epoch as baseline, indicated that this effect was limited to the P1 component with a mean latency of 161 msec. The N2P2 measure did not vary with CO exposure.

Fig. 4 illustrates temporal trends in CNV and P1 amplitude during the session. In contrast to the control group, CNV amplitude tended to decrease as COHb levels increased for both exposure groups. Larger samples are needed to evaluate the significance of this trend.

Results of this experiment are difficult to interpret because of small sample size, lack of clear behavioral differences, and paradoxical ERP findings. The large intersubject variability in miss rate within groups masked any possible group differences. Data can be normalized for individual baseline differences if an appropriate baseline measure is available. This experiment did not include a pre-exposure baseline measure. A second experiment was undertaken to correct this problem.

Table 1. Neurobehavioral Results Averaged Across Runs 2-6 for Control and CO Groups

CO, ppm	Misses	CNV, μV	N1P1, μV
0 (N=6)	6.3	8.1	13.9
100 (N=8)	4.2	10.5	17.4
200 (N=8)	6.2	6.0	19.3
95% CI	1.35	1.45	1.44
F	0.94	3.29[a]	4.18[b]

[a] p=.059 (100 × 200 ppm comparison: t=2.45, df=14, p <.05).

[b] p ≤.05 (0 × 100 ppm comparison: t=2.06, df=12, p <.10).
(0 × 200 ppm comparison: t=2.98, df=11, p <.02).

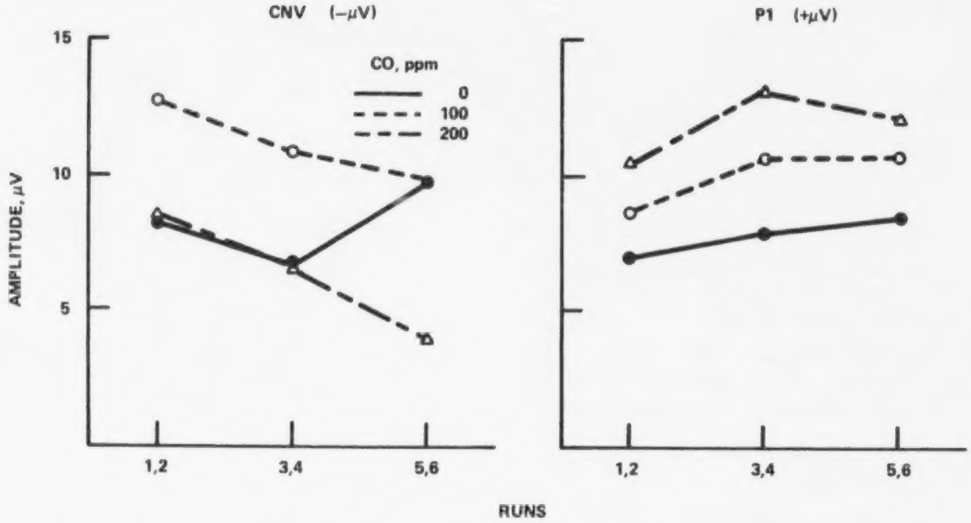

Fig. 4. Temporal trends in CNV and P1 amplitudes across time as a function of CO exposure level. Data were pooled for runs 1 + 2, 3 + 4, and 5 + 6.

Experiment II

Methods II

The behavioral task used was identical to Experiment I. To obtain a pre-exposure baseline, the testing period was lengthened to 10 runs. Run 1 was used to train subjects and run 2 served as a baseline. Subjects were given a 10-min rest break outside the chamber after run 2. CO exposure commenced with run 3.

Fifty-two nonsmoker male subjects, screened as before, were assigned double-blind to 0 (N=17), 100 (N=16), or 200 (N=19) ppm CO groups. EEG was not recorded. Blood samples were drawn before and after testing. Mean pre/post COHb levels were 0.02/0.14, 0.20/4.95, and 0.40/12.04% for 0, 100, and 200 ppm CO groups, respectively.

Fig. 5 summarizes the results of Experiment II. Differential miss scores were calculated by subtracting baseline scores (run 2) from exposure run scores. Differential scores were then averaged for each quarter of the exposure period. Fig. 5 indicates that the only striking difference between groups occurred during the initial 40 min of exposure. Control and 200-ppm groups showed a slight improvement in performance (relative to baseline) during the initial quarter of exposure, while the 100-ppm group showed an impairment in performance. A one-way ANOVA was computed for quarter I scores only [$F(2,49) = 3.845$, $p < .028$]. Mann-Whitney comparisons indicated that differential miss scores of 100-ppm subjects were higher than control ($U = 77$, $p < .05$) or 200-ppm ($U = 80.5$, $p < .02$) subjects.

Discussion

Electrophysiological data (Experiment I)

A paradoxical *increase* in amplitude of a positive component peaking at about 160 msec was observed during CO exposure sufficient to raise COHb levels to 12%. Dyer and Annau (this section) also reported increased amplitude of visual evoked potentials (EPs) in the superior colliculus of rats, but at much higher COHb levels (40%) under radically different testing conditions. On the other hand, Groll-Knapp et al. (this section) reported *decreased* amplitude of somatosensory and auditory EPs, but no change in visual EP amplitude, at COHb levels up to 10%. Moreover, Winneke et al. (this section) failed to find any change in auditory EPs at COHb levels comparable to the present study.

The lack of behavioral effects or an appropriate pre-exposure baseline confounds the interpretation of ERP results in the present study. The lack of consistency in testing and analysis procedures employed in other CO studies reported in this section further limits the generalization of results. The collective results do suggest, however, that certain ERP parameters are sensitive to CO effects under certain conditions. Further research is needed to determine the validity and functional significance of these findings.

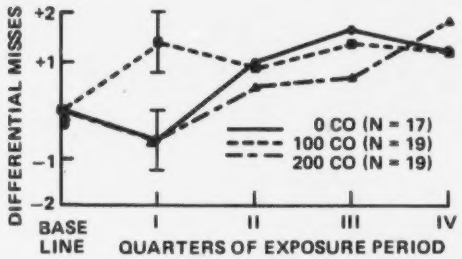

Fig. 5. Differential misses for 0-, 100-, and 200-ppm CO subjects during Experiment II. The number of misses made by each subject during pre-exposure run 2 was subtracted from misses made during each successive exposure run to obtain differential scores. The transient increase in misses during the initial 40 min of exposure (Quarter I) of the 100-ppm group was the only significant finding.

Behavioral data

CO exposure had minimal effect on performance in this study. No significant behavioral impairment was observed in Experiment I. The transient increase in miss rate observed during the initial 40 min of 100-ppm CO exposure in Experiment II may be dismissed conservatively as a sampling error (Benignus et al. 1977). Similar findings in other studies, however, suggest another possibility. Beard and Grandstaff (1975) state that behavioral decrements tend to be maximal during the initial 30 min of CO uptake. Fodor and Winneke (1972) reported a temporary vigilance decrement during the initial observation period at COHb levels of 2.3 to 3.1%. These authors suggest that a physiological compensatory mechanism could account for their results.

What evidence is available concerning the compensatory mechanism of response to CO hypoxia? Traystman (this section) observed increased cerebral blood flow and cerebral vasodilation in the rat brain during CO exposure. An analagous compensatory mechanism could enable humans to sustain normal cognitive function at COHb levels up to 20% and could explain the numerous negative reports of behavioral effects at 5 to 20% COHb levels (cf. review by Stewart 1975).

The more intriguing question concerns positive reports of behavioral impairments at COHb levels below 5% (Beard and Wertheim 1967, Fodor and Winneke 1972, Groll-Knapp et al. 1972, Horvath et al. 1971). The conflicting evidence suggests that the behavioral effects of low-level CO exposure are, at best, extremely fragile. The key to this enigma may lie in determining the threshold conditions that mediate the activation of the physiological compensatory response to CO hypoxia.

THE USE OF EVOKED POTENTIAL AND BEHAVIORAL MEASURES IN THE ASSESSMENT OF ENVIRONMENTAL INSULT

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Neurophysiologists have accumulated extensive data on evoked potentials (EPs) and behavioral responses in human suffering from a variety of organic disorders. Neurobehavioral assessment techniques, however, have not been widely used in hygienic research to evaluate the possible harmful effects of chemical and physical factors of the environment. Evoked potential methods have been used in the related field of toxicological research (Xintaras et al. 1966, Khachaturyan and Mitarevskaya 1969, Bokina and Eksler 1973, Lehotzky and Meszaros 1974).

Theoretical Basis for the Interpretation of Evoked Potentials

In accordance with current theory, the primary EP complex is considered to be a signal-releasing process because EP parameters correlate well with the intensity and frequency of external signals (Gershuni 1963, Peymer and Modin 1963, Shevelev 1971). Secondary or late EP components are associated with later processes of complex analysis and integration. The amplitude of late EP components depends on the information content of the stimulus and its meaning to the organism (Peymer 1971, Batuyev 1971, Shumilina 1971).

There is disagreement whether or not primary components of the EP reflect shifts in the general functional state of the CNS. While Khananashvili et al. (1971) answer affirmatively, Kratin et al. (1971) disagree because they observed a decrease in amplitude of early components against a background of desynchronized EEG (excitation) and during the development of extinction (inhibition) of the conditioned reflex.

Distinct changes in primary EP components appear only under extreme conditions. High 0_2 concentrations (96%) cause clear secondary alteration of the initial positive EP component in visual cortex on the second day, followed by the disappearance of this component in 3 to 4 days (Agadzhanyan and Kalyuzhnyi 1969).

In a conditioned reflex study, Shugalev (1970) distinguished three stages of amplitude change in the primary negative EP component: decrease, increase, and decrease. The first stage in the development of the conditioned reflex is characterized by reduced amplitude of late responses (Kondrat'yeva et al. 1970). During reinforcement of the conditioned reflex, primary EP components diminish and secondary components increase (Shilyagina 1971); late EP components disappear during extinction of the conditioned reflex (Shilyagina 1971).

Some authors note distinct changes in the configuration of slow potentials (SP) when amplitude, duration, and latency correlate with the animal's conditioned behavioral response. This finding emphasizes the significance of the late component of the visual evoked potential (VEP) in evaluating both the meaning of the conditioned stimulus and the functional state of various structures of the brain during a specific activity (Shumilina 1971).

The effective application of evoked potential techniques in the analysis of normal brain function requires the theoretical formulation of the origin and functional significance of individual components of evoked potentials. According to generally accepted views in the Soviet Union (e.g., Gershuni 1963, Beritov 1948, Roytbak 1955, Kogan 1956), the initial positive component reflects the postsynaptic process, i.e., excitation of pyramidal cells in cortical layers III and IV. The initial negative component is associated with excitation of superficial cortical layers. Most authors consider that this component reflects the postsynaptic potential of apical dendrites (e.g., Roytbak 1964, Anokhin 1964).

Studies of unit activity from cells in the visual cortex in response to a specific stimulus indicate that the initial discharge corresponds to the primary positive component of the VEP. The inhibitory phase, which follows discharge, coincides in part with the primary negative component of the VEP (Krondrat'yeva 1967, Polyanskiy 1965). Intercellular recordings are consistent with this interpretation; i.e., the surface negative component of the primary VEP is associated with positive hyperpolarization of pyramidal cells in the visual cortex. This component, therefore, reflects true inhibitory postsynaptic potentials. (Skrebitskiy and Voronin 1966, Fuster et al. 1965).

Amplitude of primary EP components, however, is not an absolute index of the level of cortical excitatory-inhibitory processes because these components do not vary consistently with successive changes in state. The secondary late negative wave provides a supplementary index of the functional state of the cerebral cortex. This late wave indicates both the state and location of cortical inhibition.

Evoked Potential Methods in Environmental Research

On the basis of the theoretical framework summarized above, investigators in Moscow have studied the effects of chronic exposure to neurotropic substances including formaldehyde, ozone, and carbon bisulfide on the visual evoked potential in rabbits. Primary and secondary EP components were recorded monopolarly from electrodes implanted in the visual cortex. Data were analyzed by means of Dawson's method of superposition and signal averaging with an ATAS-201 computer.

Baseline recordings were obtained 5 to 7 days after electrode implantation and again 1 week later. Animals were then placed in special chambers for treatment and were exposed continuously to a neurotropic substance for 45 days. Concentrations of formaldehyde (0.1 mg/m^3), ozone (0.05 mg/m^3) and carbon bisulfide (2.0 mg/m^3) were tested. A control group of animals were exposed to clean air under otherwise identical conditions. During the test period, VEPs elicited by arrhythmic light stimuli were recorded at 2-week intervals in special chambers, isolated from sound.

Measurements included the peak latency and amplitude of primary positive and negative VEP components, as well as the amplitude and duration of the secondary late negative wave (Fig. 1). The reliability of EP differences between baseline and exposure measures was assessed statistically. The latency of primary components remained very stable during exposures to the test substances, but the amplitude of primary components decreased differentially across time for the three substances. Dissimilar changes were observed in the secondary negative wave, although a decrease in amplitude of this component was common to all substances (Fig. 2). In brief, we found that prolonged low-level exposure to neurotropic toxicants significantly altered the temporal pattern of primary and secondary VEP component amplitudes. Neurophysiological analysis indicated, furthermore, that the changes occurred in the cortical inhibitory system.

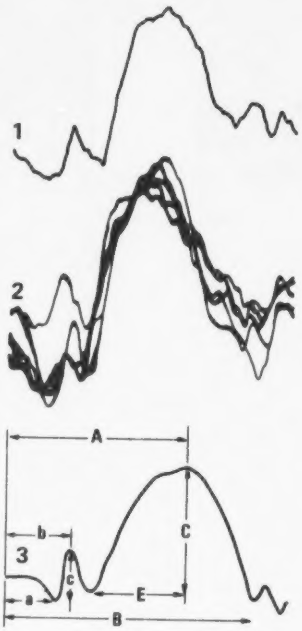

Fig. 1. (1) Typical VEP recorded from the visual cortex of a conscious rabbit in response to a single flash of light, (2) Superposition of five VEPs, (3) Schematic representation of VEP showing the method of computing amplitude-time characteristics of VEP components: a, latency of positive phase of initial response (IR); b, latency of negative IR phase; c, IR amplitude; A, slow negative wave (SNW) maximum; E, duration of SNW half-wave; B, duration of IR-SNW complex; C, SNW amplitude, Negative upwards.

Behavioral Methods in Environmental Research

Behavioral methods are used in many countries to assess the possible harmful effects of chemical and physical factors in the environment. Computer technology is employed in some laboratories to conduct simultaneous tests on a large number of animals (Weiss and Laties 1975, Guy and Chou 1975). Other simpler, but informative, methods that do not require complex computers are also used to measure the general response of an organism to environmental insult (Spyker 1975). Investigators at Kiev have also

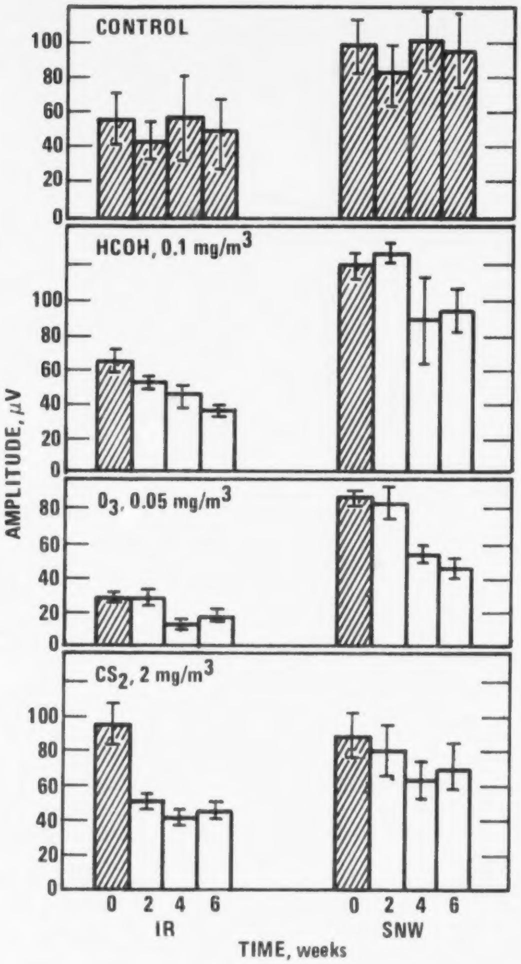

Fig. 2. Variation in IR and SNW amplitudes during 6-week inhalation of formaldehyde, ozone, and carbon disulfide in concentrations determined in the air of industrial cities. At the end of the exposure period, the amplitude of both parameters was definitely reduced. Control observations conducted in clean air for the same periods reveal the homeostatic nature of the oscillations of these IR parameters.

measured a number of behavioral parameters, including motor activity, aggressiveness, efficiency under dynamic and static load, unconditioned alimentary responses, and sensitivity to electric shock.

Although the inhabitants of technologically advanced societies are exposed extensively to electromagnetic radiation emitted by communication networks, very little is known about the physiological effects of this pervasive phenomenon. We, therefore, felt it advisable to study the behavioral effects of a superhigh frequency (SHF) field of nonthermal intensity.

Fifty male white rats were used; half were exposed to radiation and half served as controls. The source of radiation was a SHF-radiation generator with a wave length of 12.6 cm. Animals were radiated for 1 month at 500 μw/cm^2 for 7 hours a day.

Activity was measured by counting the squares in an open field that were intersected by the rat over a 3-minute test (3 times/min). Activity was measured twice at each log point (on the 9th and 10th days, on the 19th and 20th days, and so on). On the first day the activity was considered to be exploratory; on the second, motor. Aggressiveness was scored as the outcome of combat between a test and control rat following electric shock. Endurance under dynamic load was defined as the length of time the rat maintained its balance on a cylindrical rotating treadmill; endurance under static load was measured as the time the rat maintained its balance on an inclined bar at a fixed height from the ground.

The magnitude of the unconditioned alimentary response was measured as the amount of food consumed during a 20 min. period after 23 hrs. of food deprivation. Sensitivity to electrodermal shock was measured as the voltage of a 100 Hz square wave electrical stimulus needed to elicit withdrawal of the paws from the metal rods in the cage floor. Measurements were made several times prior to radiation, on days 10, 20 and 30 of exposure, and on days 15, 30, 45, 60, 75 and 90 after exposure.

Results of the study indicated a reduction in alimentary response and static and dynamic efficiency by the 10th day of radiation exposure (Fig. 3). By the 20th day of exposure, dynamic efficiency and exploratory activity were decreased and sensitivity to electrodermal shock was increased (Fig. 4 and 5). By

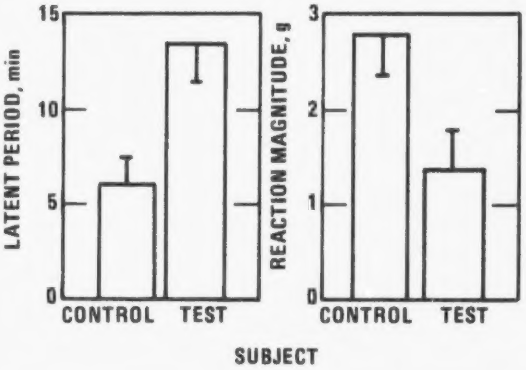

Fig. 3. Effects of SHF radiation on alimentary response in animals on 10th day of exposure.

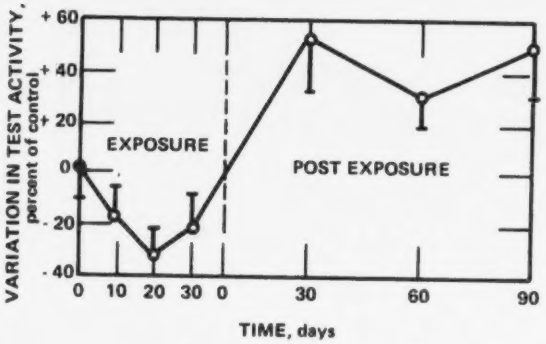

Fig. 4. Effect of SHF radiation on exploratory activity of white rats. Relative deviations of mean values of the test group from the control group and deviation errors are presented.

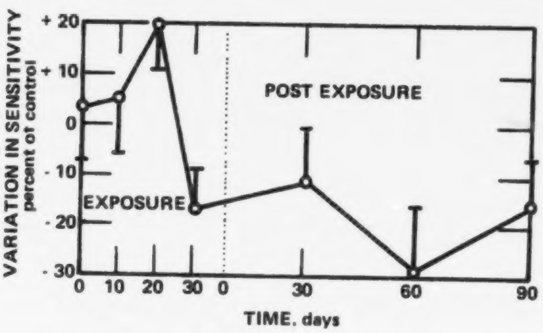

Fig. 5. Effect of SHF radiation on sensitivity to electrodermal shock.

the 30th day, exploratory and motor activity, static efficiency, and sensitivity to electric shock were reduced. In the test group, some time after cessation of exposure, signs of inhibition of the nervous system were observed: on the 15th and 30th days, the latent period of alimentary response was increased, and on the 15th day dynamic efficiency was reduced. Some variations, however, indicated excitement of the central nervous system. Exploratory activity was increased over the entire postexposure period (30th, 60th, 90th day), motor activity was increased on the 90th day, and sensitivity to electric shock was reduced on the 30th and 60th days. All the differences cited were statistically significant.

Thus, SHF radiation at 500 $\mu w/cm^2$ appears to produce inhibition of the central nervous system during radiation exposure and excitation after exposure. These general behavioral disturbances are attributed to the effect of SHF radiation on the central nervous system.

In conclusion, we found that evoked potential and behavioral assessment methods provide useful integral measures of the effect of chemical and physical environmental insults on the organism. These techniques can be employed to demonstrate subtle functional changes that are imperceptible or inaccessible by other methods of measurement.

DIAGNOSTIC UTILITY OF NEUROELECTRIC MEASURES IN ENVIRONMENTAL AND OCCUPATIONAL MEDICINE

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Formerly, occupational health was concerned with the prevention of manifest disease, while modern thinking cannot accept a work environment that causes even subclinical disorders. This development has prompted a need for sensitive and valid measurements of subclinical effects. Liver toxicity or dysfunction of the hematopoetic system can be demonstrated by traditional, well-documented laboratory tests, but in many cases first signs do not appear in the liver or blood cells. This makes those measures unsuitable in setting threshold limit values (TLVs), which aim to protect workers in occupational settings, or any individual when ambient air concentrations are concerned. In addition, many commonly used chemicals are neurotoxic at low levels in long-term exposure, and this neurotoxicity has not been taken into consideration adequately in the setting of TLVs.

In Finland, there is a definite trend toward development and application of more sensitive diagnostic techniques (Seppäläinen 1975). Neurobehavioral indices are considered valuable in the diagnosis of occupational diseases in cases that receive compensation from insurance. For example, a person who complains of subjective symptoms that decrease work capacity and who exhibits neurophysiological signs of neuropathy and/or encephalopathy and psychological impairment is considered to have an occupational disease if it can be shown that he or she has been exposed to neurotoxic chemicals.

Neurobehavioral tests have been employed several times to aid in the setting of standards and in the evaluation of working places (Seppäläinen and Tolonen 1974, Seppäläinen and Härkonen 1976, Seppäläinen et al. 1975). Relatively large groups of workers with documented exposure data, as well as controls, were studied to establish exposure-response relationships as well as noneffect levels. In this manner, neuropathy and coronary death were shown to be risks in long-term occupational exposure to 20 to 30 ppm of carbon disulfide (Tolonen et al. 1975), and the Finnish TLV was consequently lowered to 10 ppm. Various neurophysiological methods have also been applied in the study of other solvents.

Recently, several types of harmful effects on the nervous system have been reported after exposure to relatively low levels of lead. Elevated blood lead (PbB) levels (PbB 40 to 60 μg/100 ml) were found in young children who showed hyperactivity, impairment of fine motor functions, and psychological changes (David et al. 1972, Albert et al. 1974, Pueschel 1974, Landrigan et al. 1975). An association between mental retardation and lead in drinking water has also been observed (Beattie et al. 1975). Lead poisoning can cause clinical or subclinical neuropathy in both adults and children, with a slowing of the maximal motor conduction velocity (MCV) or other impairment of nerve conduction (Catton et al. 1970, Behse et al. 1972, Seppäläinen and Hernberg 1972, Vasilescu 1973, Feldman et al. 1973).

Using electrophysiological methods, investigators at the Institute of Occupational Health, Helsinki (Seppäläinen et al. 1975), detected subclinical neuropathy in 26 workers exposed to lead for 1 to 17 years in a storage battery factory. According to factory reports and a careful check of exposure history, the workers' PbB never exceeded 70 μg/100 ml. PbB determinations were evaluated in an international comparison program and were found to be valid. The main findings were slowing of the MCV of the median and ulnar nerves, particularly of the slower motor fibers (CVSF) of the ulnar nerve. Electromyographic abnormalities included fibrillations, reduction in the number of motor unit potentials during maximal muscle contraction, and abnormally long duration of motor unit potentials. Motor unit potentials are electrical phenomena recorded with needle electrodes during voluntary muscle contraction. A motor unit potential is usually a bi- or triphasic wave generated by muscle fibers that are innervated by the same anterior horn cell. The characteristics of a motor unit potential undergo different changes in myogenic and neurogenic diseases. All of these findings in lead-exposed workers were compatible with peripheral neurogenic lesion. More pronounced abnormalities have been observed in heavily exposed workers (Seppäläinen and Hernberg 1972).

The previous studies suggested a dose-response relationship between the level of lead exposure and degree of neuropathy. They also showed that slight damage within the nervous system is produced by lead during exposures hitherto regarded as safe. A more extensive study has been initiated to confirm earlier results and to determine the threshold level for subclinical neuropathy from lead exposure.

Methods

Sixty-four workers from a storage battery factory were studied (18 female). The exposure level of workers has been reliably monitored throughout their employment, and none ever showed overt clinical symptoms of lead poisoning. Subjects were divided into four exposure categories:

1. *Group A:* 38 workers who had just begun to work with lead and who had no previous history of lead exposure. Mean age was 25.9 (SD 8.1) years. Group A served as controls.
2. *Group B1:* 9 workers with occupational lead exposure from 2 to 11 years with PbB values that had never exceeded 40 μg/100 ml. Mean age was 33.6 (SD 9.7) years.
3. *Group B2:* 9 workers with lead exposure from 2 to 13 years, the highest PbB having been between 40 and 50 μg/100 ml. Mean age was 33.3 (SD 8.9) years.
4. *Group B3:* 8 workers with lead exposure from 2 to 7 years with the highest PbB between 50 and 70 μg/100 ml. (PbB exceeded 60 μg/100 ml in only one case.) Mean age was 36.5 (SD 7.6) years.

Several neurophysiological parameters were measured including: MCV of the median, ulnar, deep peroneal, and posterior tibial nerves; CVSF of the ulnar and deep peroneal nerves; and sensory conduction velocities (SCV) of the median, ulnar, and sural nerves. Nerve conduction velocities were measured using skin electrodes for stimulation and recording. MCVs were determined by standard methods (Smorto and Basmajian 1972, Seppäläinen and Hernberg 1972) with a Disa electromyograph and stimulator. A Nokia Pulse Analyser (LP4840) was used for averaging SCV responses (Seppäläinen et al. 1975).

For somatosensory evoked potentials (SEPs), the left median nerve was stimulated at the wrist with 0.2-msec square-wave pulses sufficient to elicit a clear movement of the thenar muscles. EEG activity of the right Rolandic(C4) and parietal (P4) areas, with the ipsilateral ear as reference, was amplified with an Elema Mingograph. The time constant was 0.3 sec and the upper bandpass limit was set to 70 Hz. Responses to 50 signals were averaged and further analyzed with a Wang computer.

Results

Conduction velocity data are summarized in Fig. 1. In some cases, slightly abnormal nerve conduction velocities were detected among the lead-exposed workers. Mean SCV values of the arm nerves tended to be lower among the lead-exposed groups than controls, although the difference was not statistically significant. MCV of the median nerve was lower in

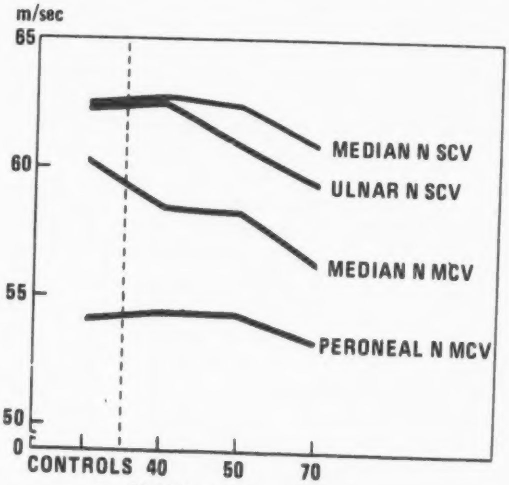

Fig. 1. Mean nerve conduction velocities at different levels of exposure among 26 lead-exposed workers and 38 controls. SCV = sensory conduction velocity; MCV = maximal motor conduction velocity. Blood lead values indicated refer to the highest blood lead recorded.

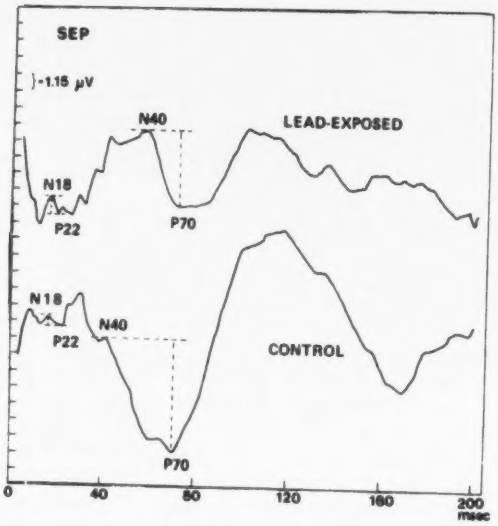

Fig. 2. SEPs of a lead-exposed subject (blood lead 65 μg/100 ml) and a control (blood lead 12 μg/100 ml) recorded at Rolandic area (C4). The measurement of peak-to-peak amplitude of N18-P22 and N40-P70 is indicated.

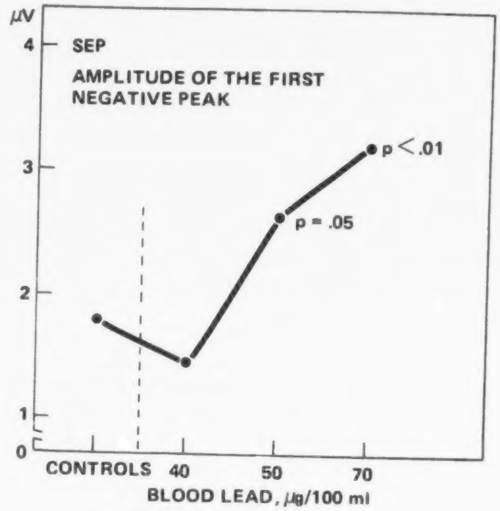

Fig. 3. Peak-to-peak amplitude of N18-P22 of the somatosensory evoked potential (SEP) on the Rolandic area (C4) among subjects with different maximal blood lead levels. The difference between the exposure groups and the controls tested with Student's t.

Group B3 than in Group A ($t = 2.42$, $p < 0.5$). No slowing of nerve conduction velocities was observed in leg nerves.

Typical SEPs observed in a control and lead-exposed subject are shown in Fig. 2. Certain group differences in SEPs were noted. Peak-to-peak amplitude measured between N18 (latency about 18 msec) and P22 (latency about 22 msec) increased directly with lead exposure level (Fig. 3). On the other hand, a later component (N40-P70, which commenced around 40 to 55 msec and reached peak around 70 to 80 msec) tended to decrease in amplitude with increasing lead exposure. Table 1 presents group means for amplitudes of both components at both recording sites. These amplitudes showed great intersubject variability. Latencies of N18 remained within a narrow range, those of the N40 component varied more, but neither of the latencies correlated with exposure.

Discussion

The occupational lead exposure of workers was relatively low and the number of subjects was small in the present study. Although some individuals showed

Table 1. Peak-to-peak Amplitudes (μV) of N18-P22 and N40-P70 on the Rolandic (C4) and Parietal (P4) Areas among Controls and among Workers Exposed to Different Levels of Lead

		N18-P22				N40-P70			
		Rolandic		Parietal		Rolandic		Parietal	
Group	N[a]	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A (controls)	31	1.76	0.92	2.86	1.66	7.90	5.85	5.68	4.24
B1	8	1.41	1.62	3.06	3.13	5.04	2.74	6.15	3.08
B2	7	2.57[b]	1.12	4.52	2.95	5.34	2.80	3.77	2.39
B3	6	3.12[c]	1.37	3.55	0.84	6.54	3.34	4.04	1.41

[a] N = number of subjects.

[b] B2 >A , $t = 2.03$, $p \approx .05$.

[c] B3 >A , $t = 3.07$, $p < .01$.

signs of subclinical neuropathy, nerve conduction velocity measures were not sensitive enough to differentiate between exposed and unexposed workers until blood lead levels exceeded 50 μg/100 ml. Only workers in Group B3, with maximal PbB between 50 and 70 μg/100 ml, exhibited significant slowing of MCV of the median nerve. This measure was previously found to be sensitive to lead effects (Seppalainen et al. 1975).

SEPs were more sensitive than nerve conduction velocities in differentiating between subjects with lead exposure and controls. Workers in groups B2 as well as B3 showed an increase in amplitude of the N18-P22 measure. This increase cannot be explained as an early sign of neuropathy, since latencies of early peaks did not increase with increasing lead exposure. Moreover, impairment of peripheral nerve function would hardly increase amplitude of early evoked phenomena; in neuropathy one would expect an opposite change, i.e. decrease in amplitude. Thus changes noted in SEPs after occupational lead exposure should be interpreted as direct central nervous effects.

Can the mechanism underlying the observed effect of lead exposure on SEPs be inferred from existing data? Several strands of evidence suggest that the increase in N18-P22 amplitude could reflect the disinhibition of central inhibitory mechanisms. Stewart et al. (1972) reported increased peak-to-peak amplitude in early components of the vertex evoked potential during human exposure to methylene chloride. This chemical solvent is metabolised to CO, which is distributed throughout the organism in the form of carboxyhemoglobin (COHb). The hypoxic effects of CO on cerebral circulation (Traystman) and neurobehavioral function (Dyer and Annau, Groll-Knapp et al., Otto et al., Winneke et al.) are described elsewhere in this volume. Germane to the present argument are the observations of increased amplitude of the vertex evoked potential in humans (Otto et al.) and the superior colliculus evoked potential in rats (Dyer and Annau) following CO exposure. Dyer and Annau attributed this finding to a "release from inhibition" produced by increased sensitivity of inhibitory synapses to hypoxia. The effect of lead on evoked potentia may be similar to the effect of CO and methylene chloride.

More direct evidence can be derived from classical observations of lead poisoning and epilepsy. Encephalopathy typically develops in severe cases of lead poisoning, and epileptic seizures are common in adult encephalopathy (Fazullah and Ramamurthi 1965; Whitfield et al. 1972; Segal et al. 1974). Epilepsy, moreover, provides a dramatic example of the pathological release of inhibitory control in the brain; masses of neurons activate simultaneously, resulting in the diffuse spread of excessive neuronal discharge (cf. Gastaut and Tassinari 1975). Low-level lead exposure is not likely to induce a "grand mal seizure" but may well exert a cumulative disinhibitory effect on CNS function reflected in increased amplitude of early SEP components.

Other evidence suggests that the hypothesized disinhibitory effect could be mediated in the thalamus. Skinner (this volume) proposes a neurophysiological model in which thalamic nuclei function as an "inhibitory gate" in sensory pathways to the cortex. N20 (probably the same as N18 in this report) has been assumed to be a subcortical response (Allison et al. 1974). Augmentation of the N18-P22 component could be caused by "release from inhibition" in the thalamic reticular nuclei, although there is no known neuropathological evidence that would implicate this thalamic area as the site of cerebral damage in lead encephalopathy. Neuropathological changes are usually diffuse when changes can be found. In fatal subacute cases in humans, conspicious increase in brain volume associated with activation of intracerebral capillaries has been found (Pentschew 1965). Dilatation of the capillaries with swelling of the endothelial cells occurs at the earliest stage. Pentschew suggested a deficit in energy metabolism resulting in chronic metabolic hypoxidosis. Thus hypoxia could be a feature common to CO and lead exposure.

Changes in SEPs suggest an effect of long-term lead exposure on brain function. Longitudinal follow-up studies on occupationally exposed subjects are needed to confirm these results. One should start with pre-exposure studies so that each could act as his own control in long-term studies.

Several preliminary ERP studies of acute exposure to neurotoxic chemicals have been described in this section. ERP changes during acute exposure may provide a useful predictor of long-term hazards to the nervous system, although long-term comparative studies are required to evaluate this possibility. Acute experiments, moreover, may not reveal the insidious cumulative effects of long-term low-level exposure. This is especially true concerning toxic neuropathy, which develops slowly at low exposure levels. Therefore, short-term and long-term studies of toxicant exposure should be undertaken in parallel.

Early detection of occupational hazards to the nervous system is vitally important to prevent irreversible damage. ERPs offer the promise of a sensitive, noninvasive predictor of chemical insult to CNS function. The functional significance of ERP changes produced by chemical exposure is difficult to evaluate, however, without more knowledge of the specific neuroanatomic substrate of event-related potentials. If a clear relationship can be established between ERP changes following acute exposure and clinical signs of encephalopathy or neuropathy following chronic exposure, ERPs will become a valuable diagnostic tool in occupational medicine. Similarly, ERP techniques would also contribute important evidence in the setting of exposure standards.

EFFECT OF CARBON MONOXIDE HYPOXIA AND HYPOXIC HYPOXIA ON CEREBRAL CIRCULATION[1]

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Several studies have shown behavioral and electrophysiological abnormalities with various levels of CO exposure (Xintaras et al. 1966a, Beard and Wertheim 1967, Fodor and Winneke 1972, Horvath et al. 1971), and it is conceivable that these effects could result from abnormalities in cerebral blood flow. The responses of various vascular beds to arterial hypoxia induced by decreasing arterial blood oxygen tension (PaO_2) (hypoxic hypoxia) has been well documented; however, circulatory responses to hypoxia induced by the administration of carbon monoxide (CO hypoxia) is less well known. The literature concerning the effects of hypoxic hypoxia on cerebral blood flow, in general, indicates varying degrees of vasodilation. Studies of CO effects on cerebral blood flow also tend to show cerebral vasodilation (Sjostrand 1948, Haggendal and Norback 1966, Paulson et al. 1973). However, many difficulties have been encountered in these experiments, such as extracranial contamination, surgical trauma to the cerebral vasculature, inadequate control of blood gas tensions, and failure to measure carboxyhemoglobin (COHb) concentrations.

A comparison of the equivalent effects of both types of hypoxia on cerebral blood flow has not been done. The concept of equivalent effects of both types of hypoxia has been described by Permutt and Farhi (1969) and involves the comparison of physiologic effects of COHb and low oxygen at equal reductions in hemoglobin, arterial oxygen content, arterial or venous oxygen tension, or blood flow. The purpose of the work described in this paper was to study and compare the effects of these two types of hypoxia on the cerebral vasculature and to define any possible differences between them. In addition, the cerebral hemodynamic response to the administration of low levels of CO was studied.

Methods

The autoperfused cerebral vasculature of 23 sodium pentobarbital (30 mg/kg) anesthetized dogs (18 to 26 kg) were studied. The comparative cerebral hemodynamic responses to CO and hypoxic hypoxia were observed in 13 animals, while the effects of low levels of CO were studied in 10 animals. Measurement of cerebral venous blood flow was made following the technique of Rapela and Green (1964). Blood flow from the confluence of the sinuses was measured after extracerebral communications had been prevented by occlusion of the lateral sinuses with bone wax (Fig. 1). Thus, intracranial blood flow from the sagittal and straight sinuses was measured. From the confluence of the sinuses, blood then passed through a previously calibrated electromagnetic flow probe, before returning to the animal via the femoral vein. With this technique, approximately 50 to 70% of the mass of the brain is drained at the confluence of the sagittal and straight sinuses. Brain perfusion pressure was estimated as systemic arterial pressure (mean) minus cerebral venous outflow pressure. Intracranial vascular resistance was calculated by dividing brain perfusion pressure by cerebral venous outflow. Cerebral venous outflow pressure and femoral arterial pressure were measured with Statham pressure transducers. Animals were paralyzed with succinylcholine and ventilated with a positive pressure respirator connected to a tracheostomy tube. Tidal volume and respiratory rate were adjusted to give an alveolar (end-expiratory) carbon dioxide of 4.0% as monitored by a CO_2 gas analyzer.

In the 13 animals in which the hemodynamic effects of hypoxic hypoxia and CO hypoxia were compared, arterial O_2 content was lowered by either of two methods: (1) by inhalation of various O_2 mixtures in nitrogen at constant ventilation; this is referred to as hypoxic hypoxia. (2) by inhalation of various levels of CO, also at constant ventilation, to produce equivalent reductions in arterial O_2 content;

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[1] Supported by ES-00454 and HL-10342.

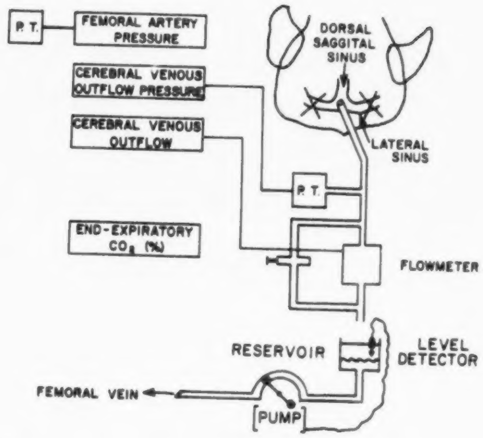

Fig. 1. Procedure used to measure cerebral venous outflow. Blood from the confluence of the sinuses (sagittal, straight, and lateral) was diverted through an electromagnetic flowmeter into a 20-ml reservoir and returned to the animal through a femoral vein by a system composed of an electronic level detector, a switch, and a pump that maintained the level of blood in the reservoir constant. Cerebral venous outflow pressure was measured upstream to the flowmeter. Collateral communications between intra- and extra-cranial venous circulations were effectively occluded by injecting bone wax into both lateral sinuses (marked with X). P.T. = pressure transducer.

hypoxia produced in this manner is referred to as CO hypoxia. O_2 content for both types of hypoxia was reduced from control (17.5 vol%) to approximately 16.0, 14.0, 8.0, and 4.0 vol%. One important point to note is that although arterial O_2 content is reduced with both types of hypoxia, with CO hypoxia there is no reduction in the arterial O_2 tension.

Animals were maintained at a given level of hypoxic hypoxia for 15 to 20 min and CO hypoxia for 35 to 40 min to allow equilibration of ventilatory and blood gases before final gas samples were taken, and to allow time for hemodynamic responses to occur and to be maintained. Arterial and cerebral venous blood samples were taken, respectively, from the femoral artery and cerebral venous outflow cannulae. The experimental protocol was such that each animal acted as its own control for several different levels of both hypoxic hypoxia and CO hypoxia. In the 10 animals in which the effects of low levels of CO were studied, COHb levels were raised to approximately 2.5, 5.5, 8.0, 12.0, 16.0, 22, 30, and 50% and maintained at each level for 30 min.

Oxygen tension, CO_2 tension, and pH at 37°C were measured immediately after the samples were obtained using IL 113 electrodes and analyzer. O_2 and COHb saturation and hemoglobin were also measured immediately after samples were taken with an IL CO-oximeter. Calibration of the electrodes was done before and after each set of samples were taken.

Results

The effects of CO hypoxia and hypoxic hypoxia on cerebral blood flow are shown in Fig. 2. (All data in Figs. 2 to 5 were analyzed for significance using analysis of variance, and a point-by-point analysis for significance was done using a paired t-test. Each point represents the mean ± SE of 13 animal preparations.) With hypoxic hypoxia, as arterial O_2 content was reduced, cerebral blood flow increased to 108, 130, 164, and 271% of control. With CO hypoxia, blood flow increased to 110, 154, 196, and 232% of control. While these increases in blood flow are significantly different from control for both types of hypoxia, there is no significant difference between the two groups. Note that while the arterial O_2 content scale refers to both CO hypoxia and hypoxic hypoxia, an additional scale showing percent COHb is also indicated.

Fig. 3 shows the effect of both types of hypoxia on systemic (mean) blood pressure. Blood pressure with hypoxic hypoxia increased to 104, 111, 114, and 108% of control as O_2 content was lowered. With CO hypoxia, blood pressure tended to decrease only slightly at the higher O_2 contents, but was significantly reduced at 4.1 vol%. Since cerebral blood flow increased equally with both types of hypoxia (Fig. 2) and considering these changes in systemic arterial blood pressure, it is obvious that cerebral vascular resistance must decrease more with CO hypoxia than with hypoxic hypoxia. This is illustrated in Fig. 4.

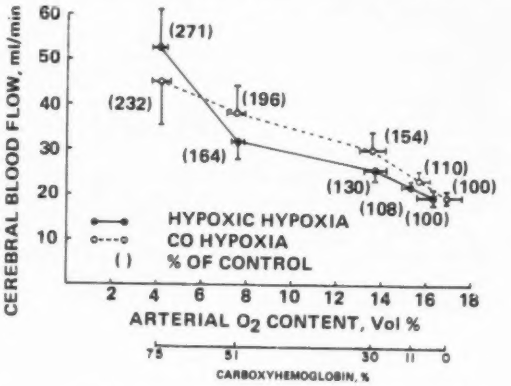

Fig. 2. Effect of CO hypoxia and hypoxic hypoxia on cerebral blood flow. Each point represents the mean ± SE of 13 animal preparations. Note that in some cases one half of the SE bar is omitted so as not to overlap other points in the figure.

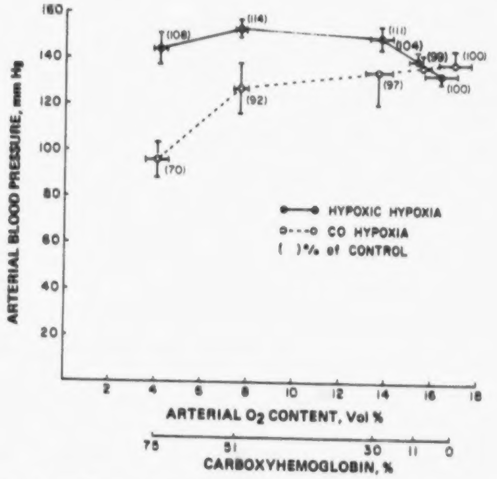

Fig. 3. Effect of CO hypoxia and hypoxic hypoxia on arterial blood pressure.

Hypoxic hypoxia resulted in a decrease in cerebral vascular resistance to 91, 85, 69, and 39% of control, while CO hypoxia produced an even greater fall in resistance to 86, 63, 47, and 30% of control. Changes from control for both curves are significant, the two curves are significantly different from each other at 13.5 and 7.6 vol%, and the difference approaches significance at 4.1 vol%. Thus, in the face of a decreased arterial O_2 content and resulting tissue hypoxia caused by both hypoxic hypoxia and CO hypoxia, the brain appears to increase blood flow in order to maintain the required O_2 delivery, as shown in Fig. 5. O_2 consumption of the brain initially increased and subsequently decreased for both types of hypoxia. The difference between the curves is not significant, although the initial increase is significant with hypoxic hypoxia, but not with CO hypoxia.

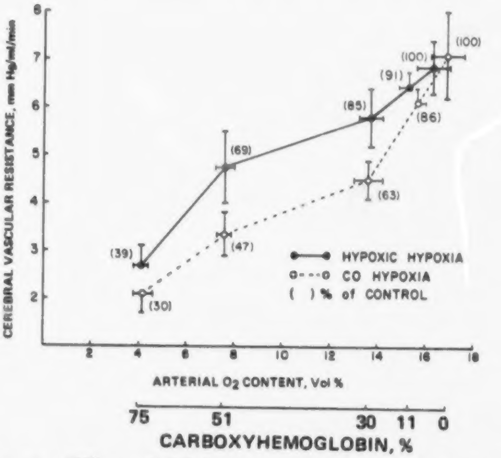

Fig. 4. Effect of CO hypoxia and hypoxic hypoxia on cerebral vascular resistance.

This increase probably results from the greater release of catecholamines with hypoxic hypoxia, which has been shown by other investigators to increase O_2 consumption (King et al. 1952, Sokoloff 1959). The de- of catecholamines with hypoxic hypoxia, which has been shown by other investigators to increase O_2 consumption (King et al. 1952, Sokoloff 1959). The decrease in O_2 consumption with hypoxic hypoxia is significant only at 4.1 vol%; with CO hypoxia it is significant at 7.6 and 4.1 vol%. These data clearly indicate that the brain can maintain oxygen consumption until rather severe levels of hypoxia.

In the second series of experiments involving 10 animals, the effects on cerebral blood flow of increasing COHb to 50% with particular emphasis on COHb levels below 20% were studied. Fig. 6 shows that a COHb level as low as 2.5% resulted in a small, but significant, increase in cerebral blood flow to 102% of control. Each point in Fig. 6 represents the mean ± SE of 10 animals, and the data were analyzed for significance by a paired t-test. With reduction in O_2 carrying capacity of 10, 20, and 30% (COHb = 10, 20, and 30%), cerebral blood flow increased to approximately 110, 120, and 130% of control, respectively. At each of these levels, cerebral O_2 consumption remained unchanged. At COHb levels above 30%, cerebral blood flow increased out of proportion to the decrease in O_2 carrying capacity, but the brain could no longer maintain constant oxygen consumption. At COHb levels of 30 and 50%, cerebral blood flow increased to about 130 and 200% of control, results comparable to the first series of experiments.

Discussion

These data support the conclusion that the brain increases blood flow in response to O_2 needs with both hypoxic hypoxia and CO hypoxia. Although the means of producing tissue hypoxia with hypoxic hypoxia and CO hypoxia are different, the results, as

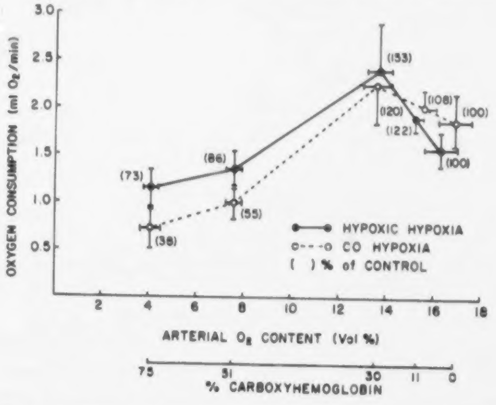

Fig. 5. Effect of CO hypoxia and hypoxic hypoxia on cerebral O_2 consumption.

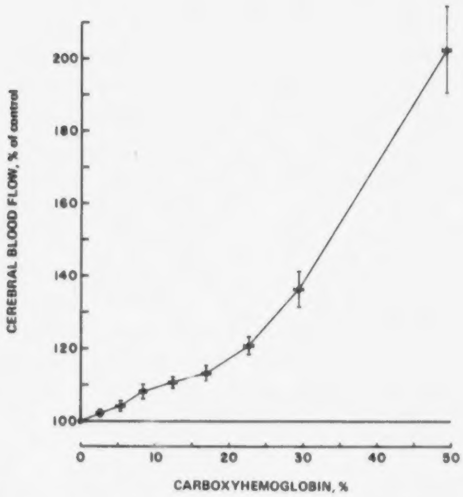

Fig. 6. Effect of increasing carboxyhemoglobin levels on cerebral blood flow, with special reference to low-level administration (below 20% COHb). Each point represents the mean ± SE of 10 animal preparations.

far as the brain's hemodynamic response, are essentially the same. The difference in the blood pressure response is accounted for by the fact that hypoxic hypoxia stimulates the chemoreceptors with its lowered PaO_2 whereas CO hypoxia does not. These pressure changes have no significant effect on cerebral blood flow since the brain autoregulates and maintains constant blood flow. The fact that cerebral responses to both types of hypoxia are similar implies that the mechanism of action of both types of hypoxia may also be similar.

The mechanism by which O_2 affects cerebral blood vessels is unclear. However, there is evidence that oxygen can act directly on isolated perfused vessels, low pO_2 in the perfusate causing vasodilation and high pO_2 vasoconstriction (Guyton et al. 1964, Detar and Bohr 1968). Hypoxia has also been reported to result in a lactacidosis and a reduction in pH of the extracellular fluid of the brain, which could result in cerebral vasodilation (Betz 1972). However, with hyperoxia, which does result in a slight vasoconstriction, no alkalosis of the extracellular fluid has been demonstrated (Betz 1972). Sokoloff (1959) pointed out that neurogenic mechanisms in the control of cerebral blood flow with hypoxia might be involved. The mechanism of the low oxygen effect on respiration is a reflex one via the chemoreceptors, and it is possible that the cerebral vasodilation with hypoxia is similarly mediated. Indeed, it has been postulated that the carotid chemoreceptors and neurogenic mechanisms are responsible for virtually all of the cerebral vasodilation in response to hypoxia (Ponte and Purves 1974). However, it has been recently demonstrated that the carotid chemoreceptors are not responsible for the cerebral vasodilator response to hypoxia (Traystman, et al. 1978, Heistad et al. 1976, Bates and Sundt 1976) to CO (Traystman et al. 1978), or to cyanide hypoxia (Pitt et al. in press). It remains possible, however, that the cerebral vasodilator responses to hypoxia are mediated through higher brain regulatory centers, including central chemoreceptors that may be located in cerebral arteries or veins, or in the brain mass itself. This matter presently remains unresolved.

The mechanism of CO-induced cerebral vasodilation differs from that of hypoxic hypoxia since arterial pO_2 with CO remains at control levels. However, cerebral venous pO_2 decreases with both hypoxic hypoxia and CO hypoxia and could be involved in a possible cerebral control mechanism. Unless an O_2 sensor that can respond to CO exists somewhere in the circulatory system, the most reasonable explanation is that brain tissue itself controls its own blood flow depending upon what the tissue requires. Since increases in cerebral blood flow with hypoxic hypoxia and CO hypoxia were essentially identical, the idea that the brain itself controls its own blood flow depending upon metabolic tissue requirements could hold for both types of hypoxia. The precise mechanism, however, by which tissue need results in cerebral vasodilation is unknown.

An important finding regarding the behavioral and electrophysiological consequences of CO exposure is that cerebral blood flow increases progressively with increasing COHb levels (Fig. 2 and 6). In addition, O_2 consumption is maintained constant even at COHb levels of 30% or more (Fig. 5). This is consistent with the finding that superior colliculus evoked potential latencies are not affected by COHb levels up to 40% (Dyer and Annau 1977). At levels above this, the brain cannot increase blood flow enough to compensate for decreased tissue O_2 delivery. At these levels, then, behavioral and neurophysiological abnormalities should be quite evident.

The idea of a threshold level below which changes in COHb would not invoke increases in cerebral blood flow (Otto and Reiter, this section) was not substantiated by these studies. A threshold level such as this would have nicely accounted for behavioral and electrophysiological decrements observed by some investigators at COHb levels less than 5% (Xintaras et al. 1966a, Beard and Wertheim 1967). Our findings show that cerebral blood flow is elevated at COHb levels as low as 2.5%. There appears to be an almost perfect compensation of blood flow as the O_2 carrying capacity is reduced, at least up to about 30% COHb.

Summary

Cerebral hemodynamic responses to arterial hypoxia were studied in 13 anesthetized dogs. Arterial O_2 content was lowered from control (17.5 vol%) to 16, 14, 8, and 4 vol% by two methods, decreasing arterial O_2 tension (hypoxic hypoxia) and increasing COHb saturation (CO hypoxia) at normal pO_2. Cerebral venous blood flow (CBF) was measured at the confluence of the sagittal, straight, and lateral sinuses, with the lateral sinuses occluded. Both hypoxic hypoxia and CO hypoxia at each of the lowered arterial O_2 contents resulted in progressive, significant increases in CBF (108, 130, 164, and 271%, and 110, 154, 196, and 232% of control, respectively). Cerebral O_2 consumption was unchanged at moderate hypoxic levels, but decreased with severe hypoxia (8 and 4 vol%).

The effects of low COHb levels (below 20%) were examined in 10 animals. It was found that COHb levels as low as 2.5% resulted in a small but significant rise in CBF. The evidence does not support the concept of a threshold level below which changes in COHb do not evoke compensatory increases in CBF.

CONTINGENT NEGATIVE VARIATION AS AN INDEX OF ENVIRONMENTAL DISTRACTION[1]

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The effects of environmental noise on performance have been generally attributed to changes in attention or arousal. When noise facilitates performance, the effect is presumed to result from an increase in attention or arousal that is not disruptive. When decrements occur, noise is presumed, conversely, to produce disruptive (i.e., excessive) increases in arousal or performance. Hockey (1970) and others have shown that the facilitory or decremental effect of noise on performance depends, in part, on the particular demands of the task.

Distraction is another concept employed to explain decremental effects of input with respect to performance of a primary task. Distraction is said to occur because of excessive increases in arousal and/or the necessity of dividing attention between two or more tasks. Tecce et al. (1969, 1973) have pointed out that distraction may be evaluated by the subject's performance with respect to the distracting task, as well as the primary task. In effect, this view assumes that distracting information, irrelevant to the primary task, is being processed and is responsible for decrements in performance of the primary task.

Electrophysiological measures of stimulus registration or information processing have also been used to assess the effects of distraction. Contingent negative variation (CNV) is presumed to reflect the degree of attention directed toward a task (Tecce and Scheff 1969, Tecce and Hamilton 1973) and to be sensitive to changes in general arousal (Tecce, 1972). McCallum and Walter (1968) have also attributed the effects of intertrial punctate tones on CNV amplitude to distraction.

In the present experiment, the CNV was employed as a measure of the distractability of a common environmental noise, the telephone ring, during a visual discrimination task. The degree of distraction was hypothesized to vary as a function of the task relevance of the distracting noise. It was hypothesized that the ringing telephone would result in reduced CNV amplitude, increased reaction time (RT), and more errors. Distractability of the telephone was also compared with distractability of random tone bursts similar to those used by McCallum and Walter (1968).

Methods

Subjects

The subjects were four male and four female paid volunteers between the ages of 18 and 39. They were paid $2.50/hr plus an incentive for each correct response. No subject had previous experience in a CNV experiment or any known neurological deficit.

Procedure

Electrical activity from the scalp and eye movements were recorded on an eight-channel Mingograph with time constants set at 5.0 sec. High-frequency filters were set at 30 Hz. Grass Ag/AgC1 disc electrodes were affixed to the scalp at Fz, Cz, Pz, T5, and T6 with collodian-soaked gauze patches. Scalp electrode impedances were less than 2 kΩ. Pairs of similar electrodes attached to the left (A1, A3) and right (A2, A4) mastoid processes served as references. Midline electrodes were referenced to linked mastoids (A1 and A2). Electrodes T5 and T6 were referenced to the contralateral mastoid (T5-A4 and T6-A3).

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[1] This work was supported by grants from the Medical Research Council of Canada; the report of these results at EPIC IV was facilitated by funds from the U.S. Environmental Protection Agency; and telephones used in this study were generously provided by British Columbia Telephone Company, Educational Division.

Beckman biopotential electrodes were placed at the nasion, outer canthus, and infraorbital ridge of the right eye and were used for bipolar recordings of EOG between nasion and outer canthus, and between outer canthus and infraorbital ridge.

EEG and EOG activity were digitized on-line by an Hewlett-Packard 2116B computer and only artifact-free trials were stored. The sampling epoch was 4.096 sec digitized into 1024 samples.

Subjects were positioned comfortably on a bed within an electrically shielded, sound-attenuated chamber. A television monitor was located in a comfortable viewing position approximately 4 meters in front of the subject. Immediately above the monitor were a red and green light to indicate the relevance or irrelevance of the concurrent auditory stimulation.

Stimulus presentation was under control of a Grason-Stadler (series 1200) solid-state programming system. Both S1 and S2 were visual stimuli presented tachistoscopically on the television monitor. A fixation point was located in the center of the monitor screen. S1 was a three- to six-letter word that could be used either as a noun only or alternatively as both a noun and a verb. Stimulus duration of S1 was 50 msec. S2 consisted of a question mark (?) presented 1.5 sec after S1. The subjects response terminated S2. Intertrial intervals varied randomly from 5 to 50 sec.

Conditions

First Standard: All subjects were given a sufficient number of trials such that eight artifact-free trials were collected. In this condition, all subjects were required to make the discrimination described above, but without distraction.

Distraction: Following the first standard condition, 32 artifact-free distraction trials were collected: trials in each of four distraction conditions were presented according to a table of random variations that ensured that an equal number (8) of trials occurred in each condition. The four conditions were designated *Relevant Tone, Relevant Telephone, Irrelevant Tone,* and *Irrelevant Telephone.* In the tone conditions, extraneous tone bursts (delivered by loud speakers below the subject's bed) began within the intertrial interval and continued through the interstimulus interval. The tone bursts commenced at variable intervals within the intertrial interval and varied randomly in duration between 100 and 1000 msec and in frequency between 640 and 2000 Hz. In the telephone conditions, a standard telephone, located near the subjects bed, began ringing in the intertrial interval and continued through the interstimulus interval. The ring mimicked the standard Bell telephone pattern of 1 sec on and 4 sec off. Both the telephone rings and the tone bursts were approximately 70 dB sound pressure level (SPL), measured at the subject's head. The relevance or irrelevance of tones or telephone rings was indicated to the subject by means of concurrent illumination of one of the two lights located above the television monitor. A green light indicated that the subsequent discrimination trial would be followed by delivery of relevant feedback, either over the telephone in the Relevant Telephone condition, or over an intercom system in the Relevant Tone condition. A red light indicated that there would be no feedback on the next trial.

Second Standard: After the distraction trials, eight artifact-free trials of a second standard condition were collected. The Second Standard condition was identical to the first in paradigm.

Instructions

The subjects were instructed to respond as quickly as possible to S2 with the left hand if the word appearing as S1 was a noun, and with the right hand if the word could be either a noun or a verb. They were also told that they would receive $0.25 for each correct response, defined as a correct choice with a latency of less that 250 msec.

In the relevant conditions, the subjects were instructed to respond to the telephone rings or to the tone bursts by picking up the telephone receiver or, if tones were occurring, by pressing an intercom call button, but only after responding to S2. After lifting the telephone receiver or pressing the intercom button, subjects were informed as to the correctness of their discrimination, the speed of their response (fast or not fast enough), and their total accumulated earnings. In the irrelevant conditions, the subjects were given the choice of terminating the tone or the telephone rings by responding in a similar fashion. If the subjects did not terminate the sounds, they were automatically terminated within 30 sec after S2. Regardless of how the noise was terminated, no information was presented to the subjects during the irrelevant conditions.

Data Reduction

The EEG from single trials, for each of the six conditions, were averaged off-line and reaction times were quantified. Baselines were defined as the averaged EEG 1.0 sec preceding S1. Averaged CNVs were quantified as mean amplitudes relative to the baseline

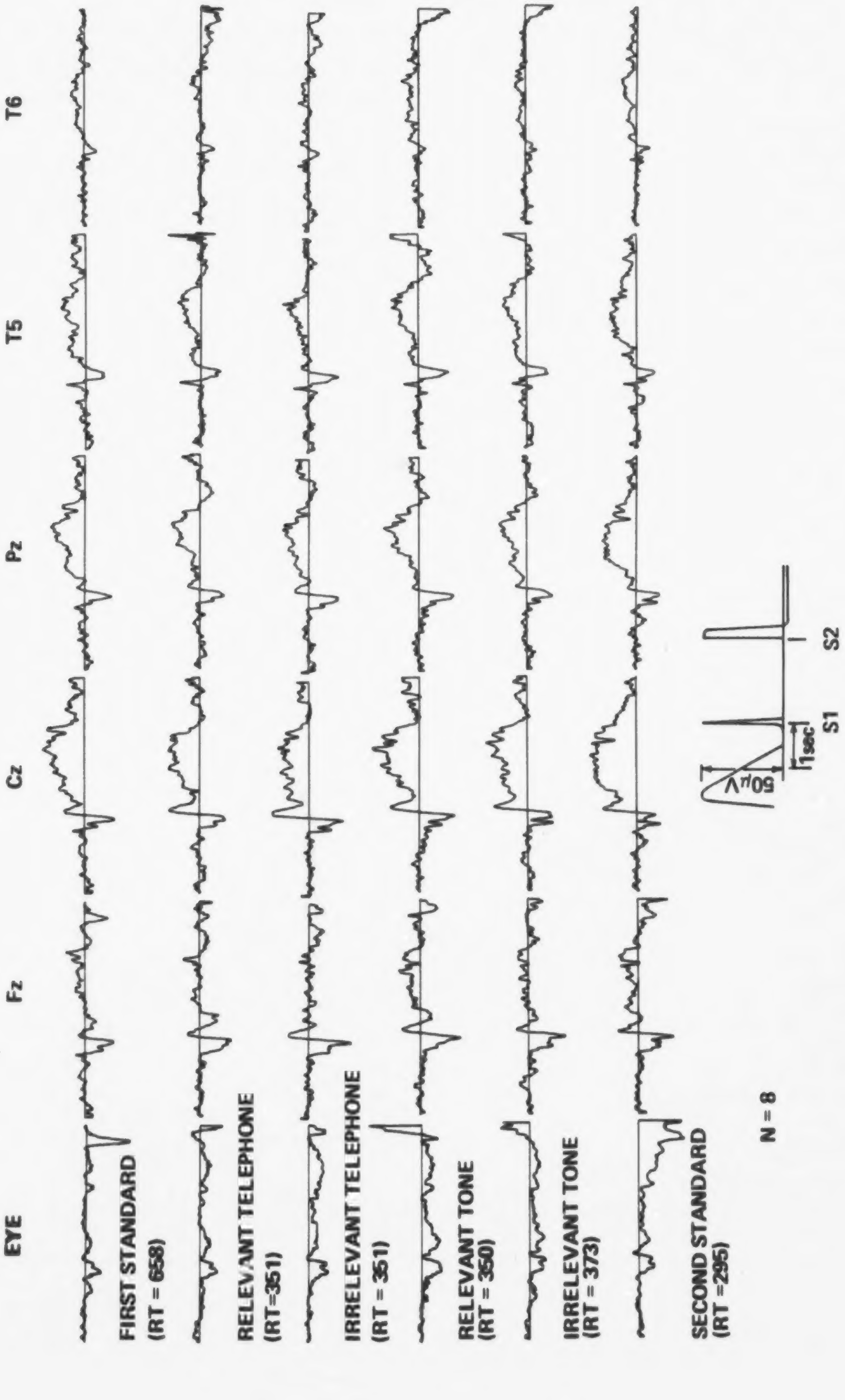

Fig. 1. Summary averages across subjects for each standard and distraction condition. Mean reaction-time for each condition is indicated in the left column.

within the following intervals: Measure 1, 500 msec following S1; Measure 2, 500 to 1000 msec following S1; Measure 3, 1000 to 1500 msec following S1; Measure 4, 200 msec preceding S2. These values were converted to microvolts by comparison to a 50-μV calibration pulse that had been averaged in an analogous manner.

Results

Summary averages across all subjects at each electrode location in each condition are shown in Fig. 1. Mean RTs for each condition are also shown in the left column of Fig. 1. A stepwise discriminant analysis indicated that ERP Measures 3 and 4 at T5, T6, and Fz were the variables that contributed most to correct classification of individual waveforms by condition.

In order to assess the effects of the four distraction conditions, repeated measures t-tests were run between conditions on the four amplitude measures for Cz, T5, and T6. The only consistent significant ($p<.05$) differences seen at Cz were between the First Standard and three distraction conditions for Measure 2 (the exception being the Irrelevant Tone condition) and between the Second Standard and all other conditions for Measure 3. In these cases, Cz amplitude was larger in both standard conditions than in the distraction conditions, and maximal in the Second Standard condition. The differences between the standard and the distracting conditions for T5 were not as consistent as those for Cz; i.e., maximal negativity was not invariably associated with the standard condition. Analysis of T6 amplitudes revealed significant differences between the First Standard and Irrelevant Tone conditions.

In view of the large contribution of T5 and T6 to the discriminant analysis, the apparent differential responsivity of T5 and T6 to distraction, and visual inspection of the waveforms, differences between T5 and T6 data were analyzed with a matched t-test design. Significant differences ($p<.05$) were found between all four measures in each condition; T5 was consistently more negative than T6.

Matched t-tests were also used to assess the effects of distraction on reaction times. Significant differences ($p<.05$) were found between the First Standard and all other conditions, between the Second Standard and the First Standard conditions, and between the Second Standard and the Irrelevant Noise conditions. RTs were longer in the First Standard than in any of the other conditions. RTs in the Second Standard were shorter than in any of the irrelevant conditions and shorter than in the First Standard condition. No significant differences in RT were found between the four distraction conditions. The number of errors in discrimination was not subjected to statistical analysis since there were almost no errors in the irrelevant or Second Standard conditions.

Discussion

One of the most interesting results of this study was the consistently larger amplitudes (greater negativity) observed at T5 compared to T6 in all conditions. Since each average contained an approximately equal number of left- and right-hand responses, and since there were no consistent differences in electrode impedances or amplifier gains, the asymmetry can presumably be attributed to the nature of the discrimination. The laterality effect implies that the two hemispheres function differentially with respect to the processing of language information presented visually.

Distraction conditions did not yield decrements in CNV amplitudes of the consistency or magnitude expected. Since reaction times were significantly longer in all distraction conditions, relative to the Second Standard, it appears that tones and rings were somewhat effective in disrupting discrimination behavior. This conclusion is, however, not supported by the minimal number of discrimination errors observed in all conditions. In general, the distractors did not severely disrupt discrimination behavior, a finding that is consistent with the minimal decrements in CNV amplitudes observed during distraction.

Although CNV decrements attributable to noise were minimal, it is notable that the differences between the First Standard and the distraction conditions, and also the differences between the Second Standard and the distraction conditions, were primarily in amplitude measures of different parts of the waveform. The First Standard differed from other conditions primarily with respect to Measure 2, the mean amplitude in the interval 500 to 1000 msec after S1. The Second Standard differed on Measure 4, which is the interval 200 msec preceding S2. These observations suggest a change of waveform shape from the First to the Second Standard conditions. This is probably attributable to the fact that the First Standard waveforms reflected primarily task acquisition processes, whereas the Second Standard waveforms reflected primarily performance processes of an already learned task.

Tecce (1972) has argued that an important measure of distraction is the degree to which distracting information is processed in addition to the effect of distraction on the primary task. This view conceptualizes distraction as information that must be processed in parallel with the primary task. This experiment did not contain any measure of the extent to which the telephone rings or tones were processed. However, the paradigm is typical of experiments in which the measure of distraction is the degree to which extraneous stimuli influence primary task performance. The observed effect was small even with distractors previously shown to produce large CNV decrements, i.e., random intertrial punctate tones (McCallum and Walter 1968). Failure to observe a behavioral or electrophysiological distraction effect may have resulted from the use of different modalities for distractors and primary task.

Is the telephone distracting? If the CNV is a reliable index of distraction, the answer appears to be "no," at least in the limited case of a visual semantic task

CARBON MONOXIDE, TRICHLOROETHYLENE, AND ALCOHOL: RELIABILITY AND VALIDITY OF NEUROBEHAVIORAL EFFECTS[1]

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Environmental toxicology is concerned with the establishment of dose-effect relations of noxious substances that may be found in human habitats. A basic objective is to provide data for setting exposure standards that will protect the health and welfare of people in residential and industrial environments. Exposure standards are based on the *threshold* at which *significant* impairment in function can be demonstrated. Environmental toxicologists are thus faced with the difficult task of defining empirical thresholds for a wide spectrum of noxious substances. Nor is it sufficient merely to show an effect; convincing evidence must be marshalled to establish that an observed effect is deleterious to health.

Evidence used in setting standards must satisfy minimal requirements of reliability and validity, basic concepts in psychological test theory (Cronbach 1961). Reliability refers to the consistency of test scores in repeated measurements, whereas validity refers to the meaning of a test score. The question of reliability assumes the form: Can observed threshold effects be replicated within or between laboratories? The question of validity underlies the need to demonstrate the functional significance of an observed impairment or effect. Reliability and validity pose critical problems for neurobehavioral research in environmental toxicology. These problems will be illustrated with experiments conducted in our laboratory during the past 3 years.

Reliability of Neurobehavioral Measures

The study of threshold effects requires extremely sensitive measures, capable of detecting small changes in the spontaneous variability or physiological "noise" of the behaving organism. Many environmental chemicals such as lead, carbon monoxide, and solvents are assumed or known to affect the central nervous system (CNS). Signal averaging techniques have been widely used to increase the signal-to-noise ratio in studies of CNS function. Therefore, average evoked potentials should provide the sensitive kind of CNS measure needed in environmental toxicology.

The functional state of the brain is influenced by numerous factors, including amount of sleep, ingestion of stimulants such as coffee or depressants such as alcohol, and motivational variables. These factors must be carefully controlled in order to distinguish threshold toxicant effects. When these factors are inadequately controlled, inconsistent or negative effects are likely to be observed.

Neurobehavioral CO research is a case in point where there is frequent nonreplication of effects between and within laboratories (Winneke 1974). Beard and Grandstaff (1975) argued that inconsistent outcomes could be attributed to variable levels of activation or arousal induced by different experimental procedures. The following experiment was designed (1) to replicate the results of Horvath et al. (1971) and (2) to test the "arousal hypothesis" proposed by Beard and Grandstaff.

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[1] The experiments reported here were supported by "Kommission Europaischer Gemeinschaften-Direction Gesundheitsschutz" (CO), and by "Deutsche Forschungsgemeinschaft" ($C_2H_3Cl_3$).

Twenty nonsmoking students participated in Experiment I. A visual vigilance task described by Horvath et al. (1971) and auditory evoked potentials (AEPs) were used as neurobehavioral measures. The vigilance task consisted of a series of 1-sec light pulses appearing every 3 sec as "nonsignals" (dimmer) or "signals" (brighter); subjects indicated choice by pressing an appropriate button. Signal brightness was preset individually at 0.9 probability of detection. Hits and false alarms (FA) were recorded. The test was conducted in two versions: a monotonous (M) and a less monotonous (LM) version. Both lasted 60 min and were preceded by a 5-min pretest, which provided a measure of detection efficiency under "alert" conditions. M was identical to the task used by Horvath et al. (1971), with 10 signals and 290 nonsignals within each of four consecutive 15 min observation periods. LM differed with respect to signal probability (30 signals, 270 nonsignals), interruptions (3 min every 15 min), and verbal feedback (subjects were informed of their performance every 15 min).

Vertex EEG, with mastoid reference, was recorded before and during the vigilance task (time constant: 0.3 sec). Clicks of 1000 Hz, 70 dB(A), and 0.01-sec duration were presented at random ISIs of 10, 18, 26, or 34 sec via earphones. AEPs were measured under "ignore instructions" before and during consecutive quarter hours of the test. Subjective states of arousal were assessed by means of 17 bipolar rating scales given before and after the experimental session. Subjects were tested single-blind either in the morning or afternoon in counterbalanced order under each of the following conditions: Control, 2.5 hr of exposure to 100 ppm CO, and 1 hr of exposure to 200 ppm subsequently lowered to 150 ppm. CO level was monitored by nondispersive infrared analysis, and carboxyhemoglobin (COHb) was determined by means of gas chromatography.

Under conditions of low CO-exposure, neurobehavioral measures were taken between average COHb values of about 3.6 and 7.5% and, under moderate conditions, between 6.5 and 11.3%. No significant CO-effect was found for hits under condition M or LM (Fig. 1).

There was a significant performance decrement over time, however ($F = 14.6$; $p < .001$). Overall false alarm rate was low. Meaningful comparisons could be made only if computations were carried out across time. Even then FAs were absent for more than half the subjects under condition M in at least one CO-condition, whereas, across exposures, there was a significant increase under condition LM ($U = 18.5$; $p < .01$). For this condition, parameters d' and β of signal detection theory (Green and Swets 1974) were determined from Freeman's tables (1964). These are given in Table 1. No significant CO effect could be shown for these more-refined performance measures.

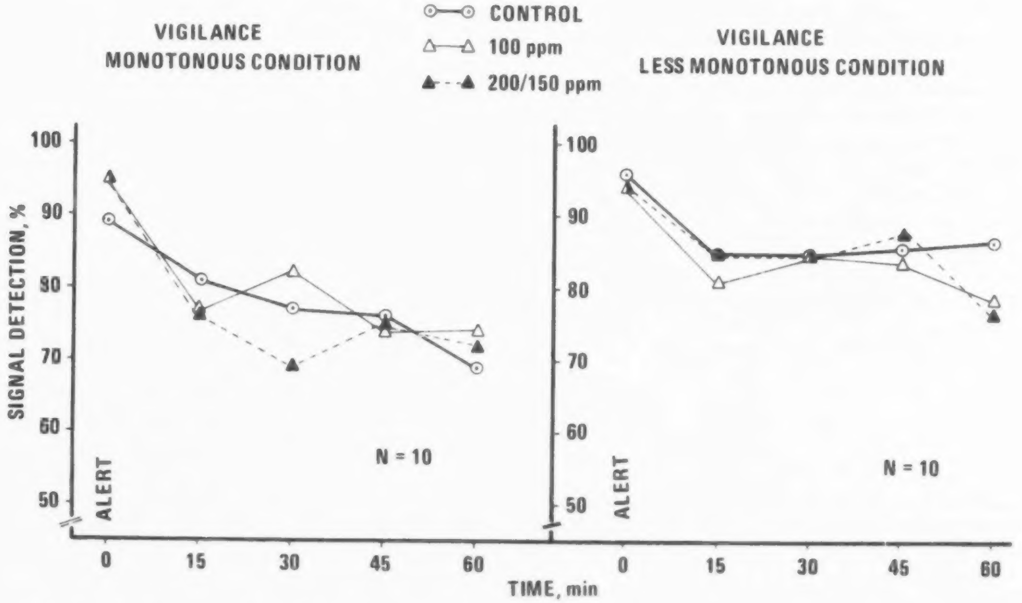

Fig. 1. Performance (% hits) in a Horvath-type visual vigilance task under two conditions of monotony and three conditions of CO exposure.

Table 1. Means and Standard Deviations of SDT Parameters d′ (Sensitivity Index) and β (Criterion) Taken from Freeman's Tables (1964). Values are for Condition LM of Experiment I.

	CO exposure		
	Control	100 ppm	200/150 ppm
d′	3.4 ± 0.5	3.4 ± 0.9	3.4 ± 0.6
β	32.4 ± 43.5	26.4 ± 17.8	44.4 ± 39.6

AEPs were measured before and during the vigilance test (Fig. 2). The first upward (negative) peak, with a latency of about 100 msec, is designated N1, and the following downward one is P2. Amplitudes were measured relative to a 200-msec prestimulus baseline. Numbers 0 through IV correspond to the respective vigilance period.

For the group as a whole, no amplitude changes for either N1 or P2 could be demonstrated under CO, and no significant main or interaction effects were noted (Fig. 3). There was, however, a significant amplitude decrement for N1 ($F = 3.8$; $p < .01$) and P2 ($F = 11.5$; $p < .001$) over time. An analysis of the bipolar rating scales revealed that the different conditions of experimental monotony did indeed induce different degrees of subjective arousal. The interaction "task duration x monotony" was of borderline significance ($p < .1$) for 9 out of the 17 items used.

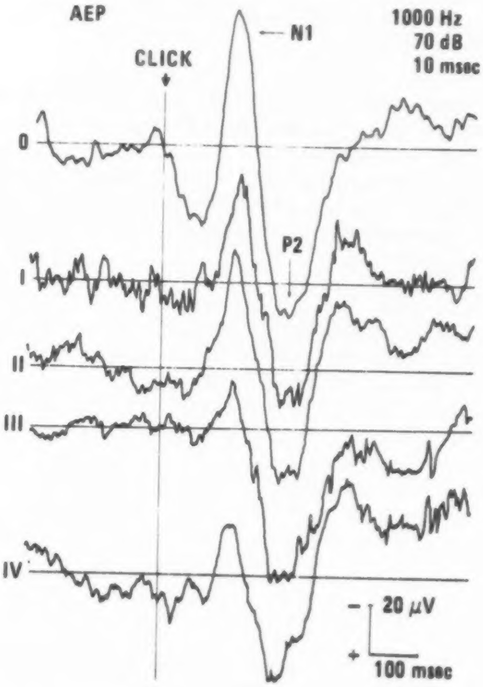

Fig. 2. Typical auditory evoked potentials (male subject, 21 years old) to 30 irregular clicks (1000 Hz, 70 dB) presented before (0) and during (I-IV) vigilance performance.

These findings exemplify the lack of test-retest reliability of CO-induced neurobehavioral impairment. We were unable to reproduce the findings of Horvath et al. (1971), although the experimental procedure was similar in both studies. In order to rule out the possibility that the presentation of clicks might have increased general arousal level, a parallel experiment without AEP measurement was conducted with 20 additional subjects. The results were essentially the same. It must be mentioned, however, that sensory restriction was more pronounced in the Horvath et al. study. Whereas Horvath's subjects sat in a dark, sound-attenuated booth (personal communication), the present experiment was run in a 15-m^3 laboratory lit by two 65-W neon bulbs with the ambient noise level-- although attenuated by earphones-- at about 67 dB(A). Therefore, the possibility cannot be ruled out that the Horvath et al. subjects were less aroused than condition M subjects, a circumstance that may have contributed to CO-induced hypoxia. For the conditions of the study presented here, however, arousal cannot be considered an important moderator of CO-related vigilance decrement. AEP measures also did not reveal any CO-influence. This finding is consistent with Hosko (1970), who did not observe any effect on visual evoked potentials below 20% COHb. Dyer (this volume) also failed to find any CO effect on superior colliculus evoked potentials below 20% COHb.

Validity of Neurobehavioral Measures

Establishment of the validity of neurobehavioral measures, assuming that the measures are in fact reliable, is a fundamental problem in environmental toxicology. A statistically significant change in evoked

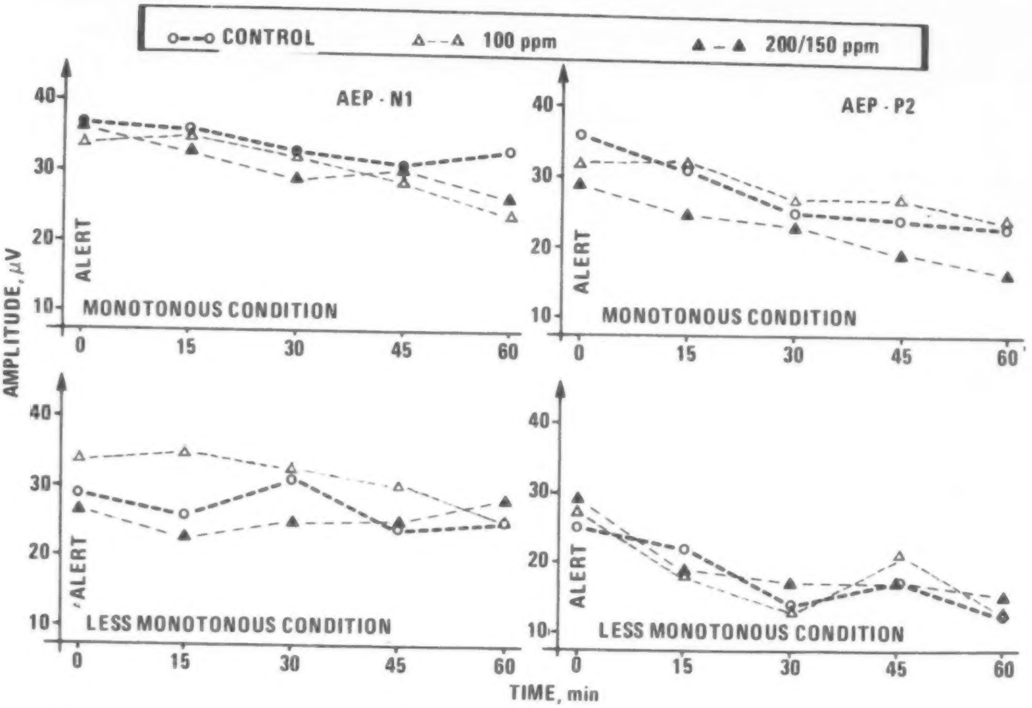

Fig. 3. Decline of amplitudes of AEP components N1 and P2 over time for two conditions of monotony and three conditions of CO exposure. Means are based on 10 subjects each.

potential amplitude or latency produced by toxicant exposure is not a sufficient index of validity, unless the biological or behavioral significance of the electrophysiological effect can be demonstrated. The significance of behavioral impairments is generally self-evident, although the predictive validity of behavioral measures is rarely tested. For example, a vigilance decrement experimentally induced by exposure to a noxious aerosol can be extrapolated to real life. The validity of evoked and slow brain potential measures, however, is difficult to demonstrate because the physiological significance of these measures is still obscure. The meaning of observed changes in brain potentials must be inferred from concurrent behavioral measures or changes induced by chemical compounds of known pharmacological properties such as alcohol. This procedure, known as convergent validation, will be exemplified by two closely related experiments.

Experiments II and III deal with the neurobehavioral effects of trichloroethylene ($C_2H_3Cl_3$), an industrial solvent with narcotic properties, and alcohol. In Experiment II (Winneke and Kastka 1974), 18 volunteers were exposed for about 3 1/2 hours to 50 ppm $C_2H_3Cl_3$. Vigilance performance was measured with a bisensory task designed to produce a high false alarm rate (FAR). In two sessions of 50-min duration, subjects had to monitor auditory and visual events in order to detect "signals" that were shorter than other events. Neutral events were 500-msec duration; critical ones were 200 (Experiment II) or 150 msec (Experiment III) shorter. This test started 77 min after the beginning of the experiment and lasted 100 min.

Auditory evoked potentials (AEP) were computed from vertex EEG, with mastoid reference recorded just before and after the vigilance test. A regular sequence (ISI = 2 sec) of fifty 1000-Hz tone bursts of 30-msec duration was presented via earphones. Subjects were instructed to respond by button press to signals that were slightly weaker than the majority of events. Two signals were randomly distributed among 50 bursts. Baseline-to-peak measures were taken for components N1 and P2 as described above.

The methodology of Experiment III (Winneke and Kastka 1975) was identical to Experiment II. Twelve subjects were tested in each of the following conditions: Control, 0.6 g alcohol/kg, 3 1/2 hours of exposure to 50 ppm $C_2H_3Cl_3$ and alcohol plus $C_2H_3Cl_3$. Ethyl alcohol was given in orange juice just before the vigilance task. Blood alcohol level was

24 mg% on the average at the end of the experiment, and, with an hourly decrease of 15 mg% assumed, is estimated to have peaked at 50-60 mg%.

A review of vigilance performance indicates that the experiments differed in task difficulty (Table 2). The signal-to-noise ratio was 300/500 msec for Experiment II, whereas it was 350/500 msec in Experiment III. Hits and FAR differed in the expected duration. This was also true for the sensitivity index d′, which was clearly lower in Experiment III. As for vigilance performance, there apparently was no $C_2H_3Cl_3$ effect on hits, but there was a marked effect if hits and FARs were combined to yield d′. Interestingly enough, there was a significant increase in sensitivity under the influence of $C_2H_3Cl_3$ as compared to control values in Experiment II but a slight, insignificant decrease in Experiment III. This unexpected reversal suggests a possible interaction between task difficulty and prenarcotic action of $C_2H_3Cl_3$; for easy detection conditions, subjects may have been able to compensate or even overcompensate for the $C_2H_3Cl_3$-induced handicap, whereas under more threshold-like conditions (Experiment III), compensation may have broken down.

This interpretation rests mainly on the results of AEP measurements shown in Table 3. There was little change in amplitude from beginning to end of the experiment for control conditions, whereas there was a marked amplitude decrement for component P2 after 3 1/2 hours of $C_2H_3Cl_3$ exposure. There was a slight increase of P2 amplitude from first to second testing under control conditions, but a marked reduction after $C_2H_3Cl_3$ exposure. The resulting interaction "time x condition" was significant for $C_2H_3Cl_3$ in both experiments ($p < .05$), but of only borderline significance ($p < .12$) for the alcohol condition of Experiment III. There was no consistent effect on N1 amplitude of $C_2H_3Cl_3$ or alcohol.

While the results of Experiments II and III demonstrated test-retest reliability of the $C_2H_3Cl_3$-induced decrement in P2 amplitude, the electrophysiological and behavioral data were inconsistent across experiments. $C_2H_3Cl_3$ exposure was associated with increased sensitivity (d′) in Experiment II, but with no significant change of d′ in Experiment III. The effect of alcohol on AEPs and behavior was also equivocal: alcohol produced a pronounced vigilance

Table 2. Vigilance Performance for Experiments II and III.

	Experiment II[a] (N = 18)		Experiment III[a] (N = 12)		
	Control	$C_2H_3Cl_3$	Control	$C_2H_3Cl_3$	Alcohol
Hits, %	71.3	73.1	56.7	56.5	49.1[b]
FAR, %	1.2	1.0	2.9	3.2	2.9
d′	3.0	3.2[c]	2.4	2.2	2.0[c]
β	11.3	9.1	11.5	10.1	10.6

[a] For definition of conditions, see text. Significance refers to respective control value.

[b] $p < .01$.

[c] $p < .05$.

Table 3. Amplitude (μV) of AEP Component P2 for Experiments II and III.

	Experiment II (N = 14)[a]		Experiment III (N = 12)	
	Beginning	End	Beginning	End
Control	17.6	20.8	19.0	20.9
$C_2H_3Cl_3$	19.3	15.6[b]	21.1	19.1[b]
Alcohol	-	-	20.3	18.6

[a] Four protocols were disturbed and could not be used.

[b] $p < .05$ for interaction "time x exposure" as compared to control.

decrement, but only a borderline P2 decrement (Table 3). Thus, the validity of observed electrophysiological effects could not be demonstrated with respect to available behavioral measures. That is, we are confronted with a reliable electrophysiological effect, the meaning of which remains obscure.

These findings illustrate a dissociation of behavioral and electrophysiological changes under the influence of $C_2H_3Cl_3$ and alcohol. Similar dissociations have been reported by others (Clark et al. 1969, 1970), although these have been criticized on the grounds that behavioral and neurophysiological measures were taken in different sets of trials, under different instructions, and with inadequate control of attentional variables (Donchin and Sutton 1970, Paul and Sutton 1973). The data reported here are open to similar criticisms because vigilance performance and AEPs were, indeed, measured in different parts of the experiment. Attentional variables, however, were controlled by essentially the same instructions for vigilance and AEP measurements.

Implicit in this discussion is the assumption that there ought to be a direct relationship between the parameters of CNS function and behavior chosen for comparison. The observed dissociations raise doubts about the validity of this assumption, particularly under conditions of toxicant exposure.

Conclusions

Basic problems in assessing the reliability and validity of neurobehavioral measures have been examined in the context of data gathered during human exposure to environmental toxicants. The extensive, but contradictory, literature concerning the neurobehavioral effect of low concentrations of carbon monoxide was used to illustrate the problem of reliability. Our failure to replicate the findings of Horvath et al. (1971) adds another increment of uncertainty to the CO story, although these results indicate that variation of arousal level within the normal waking range does not moderate the neurobehavioral effect of CO-induced hypoxia as hypothesized by Beard and Grandstaff (1975). The possibility remains, however, that detection of subtle CO effects may be enhanced during extreme states of hypo-arousal that occur during deep sleep (Groll-Knapp et al., this volume), prolonged vigilance performance, or sensory deprivation.

Large differences in individual susceptibility to CO poisoning may also contribute to the confusion. Most investigators, including the present authors, computed means across subjects, thereby obscuring possible individual differences in CO responsivity. It is possible, for instance, that the normal adult population contains a bimodal distribution of CO responders who show decrements in performance and nonresponders who show no decrements. The reliability of individual differences in CO susceptibility needs to be assessed, and, if such differences are established, the distinctive features of CO-responders need to be identified.

Another criticism concerns the subject population used in most human neurobehavioral CO studies. Young healthy adults are probably the least likely segment of the population to show deleterious effects during low-level exposure. The ability of humans and animals to compensate for CO-induced hypoxia up to COHb levels of 20% is well known (Dyer and Annau, this volume). Data from Traystman (this volume) and others suggest that increased cerebral bloodflow compensates for the reduced supply of oxyhemoglobin. Populations with reduced oxygen uptake—e.g., elderly persons with presumed slight impairment of cerebral circulation—are likely to be far more susceptible to CO effects than young, healthy adults.

Establishment of the validity of ERP measures in environmental toxicology and other clinical applications will probably remain a thorny problem for some time to come. The process of validation entails the correlation of a known criterion measure with an unknown test variable. In the present discussion, we have assumed that behavioral measures (i.e., vigilance performance) constitute meaningful criteria for the validation of ERP measures. While a remarkable correspondence between performance and certain ERP components such as the P300 has been demonstrated (see review by Tueting, this volume), the correspondence is relatively poor for other measures such as reaction time and CNV amplitude (Rebert and Tecce 1973). The assumption that vigilance performance constitutes a meaningful criterion for the validation of P2 changes observed during toxicant exposure is therefore questionable. If the behavioral and electrophysiological measures show parallel changes, a straightforward interpretation of the data can be made, but, if the two measures are dissociated, the validity of the ERP measure cannot be evaluated.

What conclusions may be drawn from the data in view of this dilemma? Although the evidence of dissociation is equivocal, the results suggest caution in extrapolating from control to exposure conditions. Alcohol, anesthetic agents, or other environmental toxicants may decouple the relationship between ERP measures and performance observed under normal conditions. This problem is not unique to environmental toxicology. Normal brain-behavior relations may be disturbed by a variety of clinical disorders or pharmacological interventions, and the effects must be examined carefully in each case.

Event-related potentials are not understood well enough at present to be accepted as independent evidence in evaluating the health effects of environmental toxicants. Validation of ERP measures, as described here, will require a systematic effort to study brain-behavior relations in a variety of normal and abnormal conditions in order to establish an extensive network of empirical associations. This network will eventually provide the frame of reference necessary to understand the significance of ERP changes observed without concurrent behavioral measures.

DISSOCIATION BETWEEN TIME COURSE OF ACETYLCHOLINESTERASE INHIBITION AND NEUROPHYSIOLOGICAL EFFECTS OF PARATHION IN RAT AND MONKEY[1]

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Parathion (*O,O*-diethyl *O-p*-nitrophenyl phosphorothionate) is an insecticide with widespread current use and high mammalian toxicity. Cholinergic symptoms and death due to parathion poisoning have been attributed to acetylcholinesterase (AChE) inhibition by paraoxon, the active toxic metabolite of parathion (O'Brien 1967). In this study, the time course of inhibition of AChE activity in the central nervous system (CNS) and blood after parathion administration was compared with the time course of neurophysiological effects, as measured by visual evoked potentials (VEPs) in rats and monkeys bearing chronically implanted electrodes and by changes in the maximal electroshock seizure (MES) pattern in rats. The results suggest either that adaptation or tolerance to continued AChE inhibition occurs or that the cholinergic symptoms of parathion poisoning are due to an effect other than AChE inhibition. Other possibilities for mechanisms of action are suggested.

Effects of parathion administration on VEP, MES, and AChE inhibition in rats

Effects of a single dose of parathion on the VEP were determined in eight rats with electrodes chronically implanted in cortical and subcortical brain areas. Parathion was dissolved in polyethylene glycol (Carbowax 300) and administered subcutaneously (sc). Rats were recorded awake and unrestrained in their home cages. Potentials were elicited by light flashes at 1/sec from a Grass photostimulator. Responses were recorded from side-by-side bipolar electrodes with 1-mm vertical tip separation. Each VEP included fifty responses averaged with a Northern Scientific computer. Usually six averaged VEPs were recorded from each brain area at each time period. Computer readout was with a Moseley X-Y recorder.

The effects of 3 mg/kg parathion sc on the averaged VEP in the visual cortex (Fig. 1) were to increase the latency and decrease the amplitude of the first major wave. Effects were maximal 2 and 4 hr after administration; 8 hr after administration the response had fully recovered. Responses recorded in the superior colliculus under the same conditions showed even more dramatic effects of parathion administration (Fig. 2). Collicular VEP was almost completely eliminated 45 min and 2 hr after 3 mg/kg sc parathion. Recovery was rapid, and by 4 hr after dosage the response was back to normal.

The effects of another cholinergic agent, tremorine, on VEPs in the rat were determined and compared with the effects of parathion. Tremorine is converted to oxotremorine, which acts primarily to stimulate central cholinergic receptors. The effects of a single 5- or 10-mg/kg dose of tremorine injected intraperitoneally (ip) were to increase the latency and decrease the amplitude of averaged VEPs recorded from the primary visual cortex. These effects were nearly identical to those produced by parathion. This suggests that these effects may reasonably be attributed to central or peripheral (or both) cholinergic actions. Histological evidence for involvement of central cholinergic synapses in VEP generation has been provided by Shute and Lewis (1967), who have described

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[1] Supported by NIH grant ES-00163.

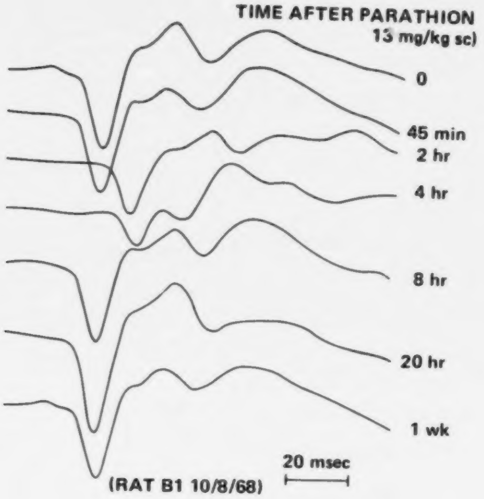

Fig. 1. Effects of parathion on VEPs in the visual cortex of an unanesthetized, unrestrained rat with chronically implanted brain electrodes. Latency was increased and amplitude was decreased 2 and 4 hr after parathion injection. Recovery was complete after 8 hr.

AChE-containing fibers rising from the brainstem and passing via the dorsal tegmental pathway directly and indirectly to the superior colliculus, lateral geniculate body, and pretectal area.

The puzzle of these observations is not so much the marked effects of the toxin on the VEP but the rapid recovery of the response. Parathion administration is believed to result in irreversible or only slowly reversible inhibition of AChE activity in the CNS (O'Brien 1967). However, some controversy exists regarding the rate of recovery of brain AChE activity after parathion administration in the rat. Although an early report described recovery of brain AChE activity 4 hr after administration of parathion (DuBois et al. 1949), another observed that several days were required for 60% recovery from inhibition (Davison 1953), and a more recent report (Giachetti et al. 1966) stated that 1 month was required for complete recovery after parathion administered on alternate days for 4 months.

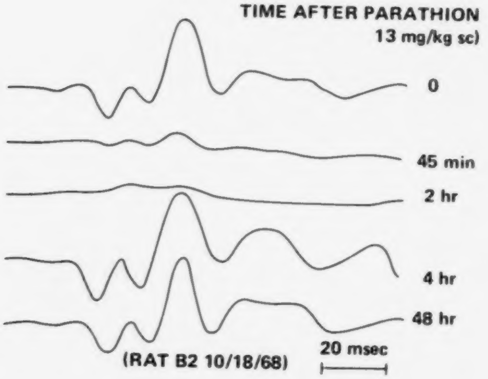

Fig. 2. Averaged VEPs in the superior colliculus of the rat. The response was nearly abolished 45 min and 2 hr after injection of parathion, but recovery was complete at 4 hr.

We therefore undertook an investigation of the time-course of AChE inhibition and recovery after parathion administration in the rat. AChE activity was measured using a colorimetric method (Ellman et al. 1961). A single dose of 2.0 mg/kg parathion was administered ip or sc in separate experiments with essentially similar results (Fig. 3). Inhibition of AChE activity in the caudate nucleus, cerebral cortex, brainstem, spinal cord, and blood, and inhibition of plasma pseudocholinesterase (ChE) activity occurred rapidly; peak inhibition was reached 4 to 9 hr after administration. AChE inhibition occurred more rapidly and was greater in blood than in CNS. Recovery of blood AChE and of plasma ChE activities was rapid and complete during the 1 week of this study, whereas AChE activity in the CNS showed no evidence of recovery during this time. In an additional study, it was found that 2 to 4 weeks were required for complete recovery of AChE activity in the CNS after approximately 40% inhibition following injection of parathion.

Comparison of Figs. 1 to 3 reveals that recovery of VEPs in the brain occurred long before recovery of brain AChE activity. VEP changes after parathion administration occurred only during the falling phase of AChE activity. By the time brain AChE activity had reached peak inhibition and stabilized at this inhibited level, VEPs had recovered.

To determine if another measure of CNS function recovered as rapidly after parathion administration as the VEP, the effects of three dose levels of parathion on the durations of the various phases of the maximal electroshock seizure (MES) were investigated. To produce MES, silver disc electrodes with a small amount of electrode paste were placed on the scalp on top of the head just in front of the ears, and a sine wave (60 Hz) stimulus of 250 mA was delivered for 0.2 sec by a constant current stimulator, as described previously (Woolley 1970). Administration of 1.5, 2.0, or 2.5 mg/kg parathion ip in a single dose significantly altered the MES pattern 1 hr later, but the changes were greater at 4 hr (Fig. 4). Recovery had occurred by 24 hr. The principal effects of parathion administration were to increase the duration of

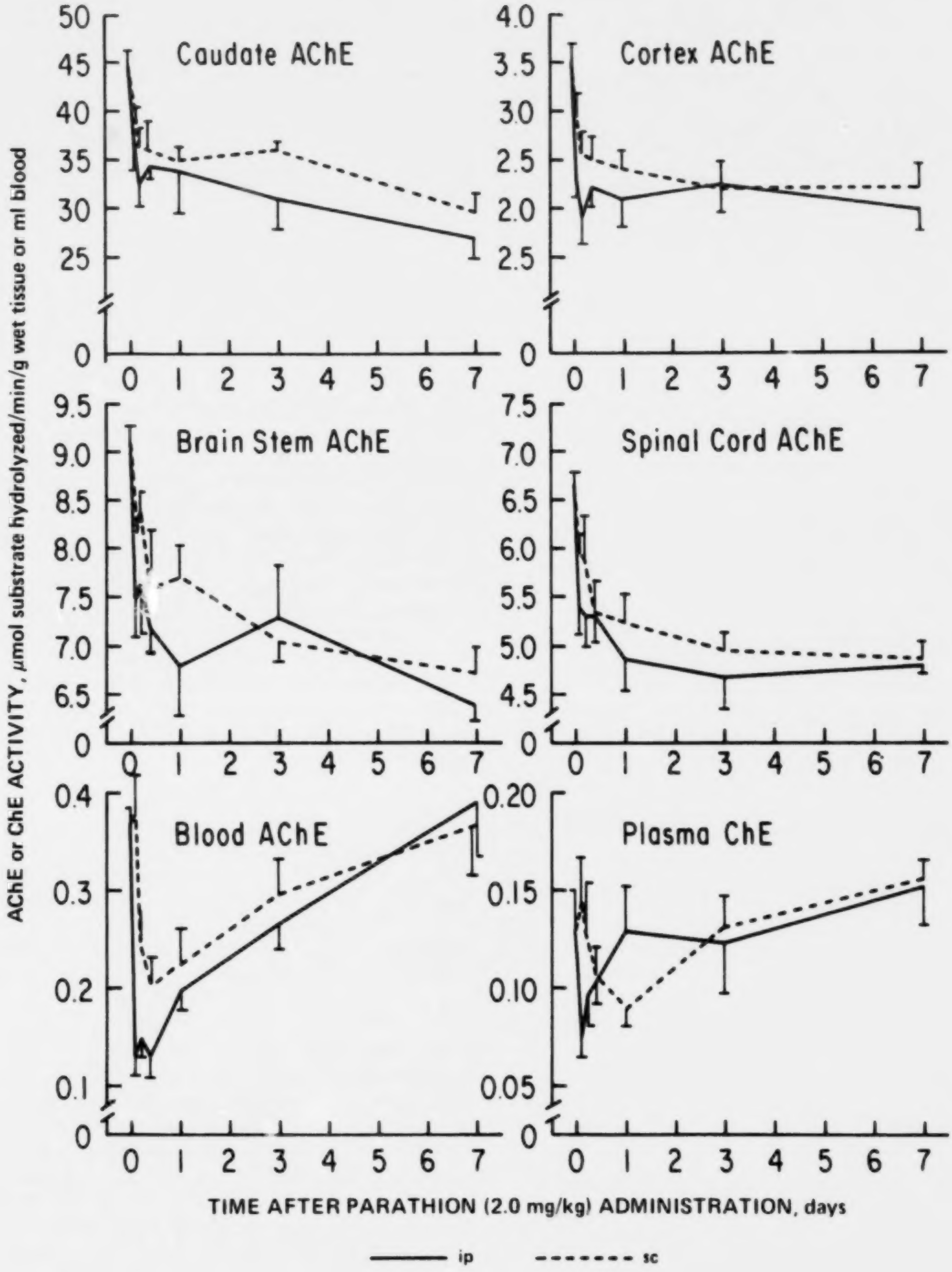

Fig. 3. AChE and ChE activities after parathion administration in the rat. Enzyme activities in blood and CNS were rapidly inhibited after administration. Recovery was fairly fast in blood and returned to control levels by 1 week, whereas AChE activity in the CNS showed no recovery during this same time.

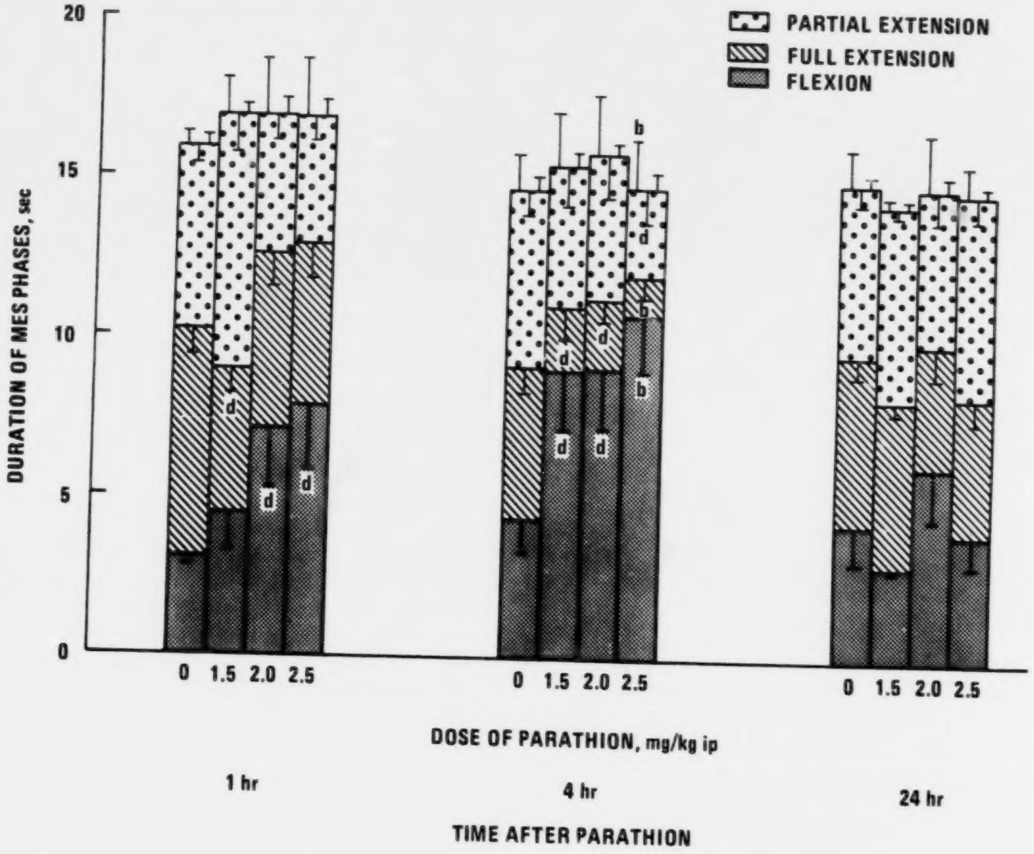

Fig. 4. Durations of phases of the maximal electroshock seizure (MES) were altered 1 and 4 hr after parathion administration in the rat but had returned to normal at 24 hr.

the initial tonic flexor phase and to shorten the duration of the following full extensor phase. There was no effect on the total duration of the seizure. Other work in our laboratory (unpublished) indicated that tremorine administration produced changes in duration of MES phases similar to those produced by parathion administration; thus, these MES changes may be typical of at least some cholinergic agents.

Other studies (Woolley 1976) showed that administration of scopolamine, but not of methylscopolamine, blocked the effects of parathion on the MES. Because methylscopolamine has marked peripheral anticholinergic effects but little central effects, whereas scopolamine has both central and peripheral anticholinergic effects (Innes and Nickerson 1975), these drug-parathion interaction studies demonstrate that the effects of parathion on the MES are due to an action on the CNS.

The results of the studies of the effects of parathion on the MES emphasize again that the effects of parathion administration on some aspects of CNS function may disappear before CNS AChE activity recovers.

Effects on VEP, visual discrimination, and cortex AChE activity in monkeys

Study of the effects of parathion may have significance for human health. However, for that purpose, use of the monkey as a model would appear to be more relevant than use of the rat. For this reason, studies were undertaken to determine the time course of effects of parathion on brain electrical activity, on blood and brain AChE activities, and on performance of a visual discrimination task. Effects on brain electrical activity were determined in three bonnet

(Macaca radiata) and two rhesus *(M. mulatta)* monkeys, each with 16 chronically implanted monopolar cortical surface electrodes. The indifferent electrode was located in bone over the frontal sinus. The animals were placed in primate restraining chairs during the recording sessions. VEPs were elicited by flash as in the study with rats, except that evoked potentials from six electrode positions were averaged simultaneously by a Data General, Nova 1200, programmable computer. In some cases, the averaged potential, plus and minus the standard errors of alternate mean values (Fig. 5), were also calculated. The behavior of the animal during a recording session was monitored via closed-circuit television.

The effects of parathion were essentially similar for VEPs recorded in various locations in the primary and association visual cortical areas. The major effect was to increase latency, whereas effects on amplitude were variable. When 4 mg/kg parathion was administered orally (po) in fruit, significant increases in latency were evident 3 or 4 hr later, were maximal at 6 to 7 hr, usually showed some improvement at 10 to 12 hr, and had returned to pretreatment values by 24 to 48 hr after administration (Fig. 5).

Simultaneous measurements of blood AChE activity and VEP (e.g., Fig. 5) showed that, after 4 mg/kg parathion, AChE activity in blood fell rapidly during the first 4 hr, reached maximal inhibition by about 7 hr, and showed some recovery of activity by 24 hr. However, at 48 hr, when VEPs had usually recovered and the animals were obviously feeling better, blood AChE activity had only recovered about 50% over the peak inhibited levels.

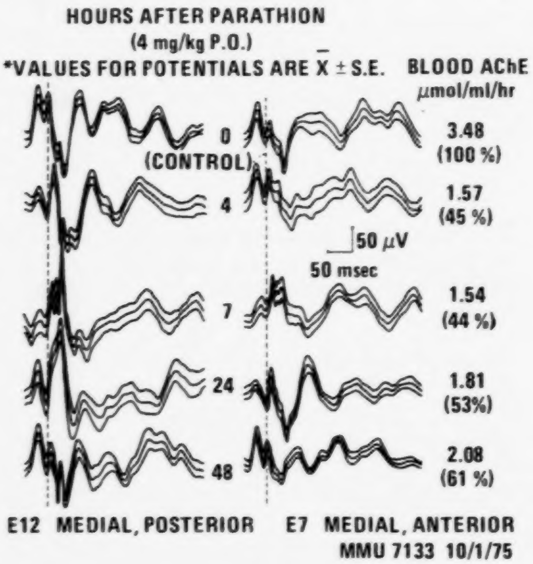

Fig. 5. Averaged VEPs with ± S.E. recorded from the visual cortex of a monkey. Effects of parathion were most marked 7 hr after administration. Some recovery was evident at 24 hr, and responses were back to normal at 48 hr.

An attempt was made to determine the degree of inhibition and recovery of brain AChE activity in three monkeys after administration of parathion. Biopsy samples weighing about 30 mg were taken successively from adjacent areas of parietal cortex 2 weeks before, 2 days after, and 8 or 14 days after administration of a single dose of 3.0, 4.0, or 5.0 mg/kg parathion sc (Fig. 6). Blood samples for AChE activity were taken more frequently. Peak inhibition of blood AChE activity occurred about 2 days after injection, which was considerably later than the time of peak inhibition after po administration. At the times of peak effect, blood AChE activities were 8, 26, and 32% of control activities after 5.0, 4.0, or 3.0 mg/kg parathion, respectively. On the other hand, cortex AChE activities in the same animals were 30, 64, and 102% of control values 2 days after parathion administration. The animal showing the greatest inhibition died at 8 days, and brain AChE activity showed essentially no recovery at this time. (Autopsy revealed that death was due to intestinal blockage.) In the remaining two animals, brain AChE activity showed no change at 14 days compared with values 2 days after parathion, whereas blood AChE activity had shown significant recovery.

When these studies in the monkey are compared, it is evident that, as in the rat, the effects of parathion on VEPs were of relatively brief duration compared with effects on brain AChE activity.

In previous work (Reiter et al. 1975), administration of 2.0, 1.5, and 1.0 mg/kg parathion abolished performance of learned visual discrimination performance in three rhesus monkeys 5 hr later and for as long as 3 to 7 days. When performance of the tasks returned after the 2.0 mg/kg dose, the level of performance remained below pretreatment values for up to 3 weeks. A dose of 0.5 mg/kg did not affect performance. Thus, effects of parathion on behavior lasted considerably longer than did effects on VEPs.

Possible explanations for the dissociation between changes in VEP and AChE inhibition

The present findings show that after parathion administration changes in VEPs occur during the falling phase of AChE activity, but that despite continued inhibition of AChE activity the CNS effects disappear. This may be interpreted to mean that development of adaptation or tolerance to depression of

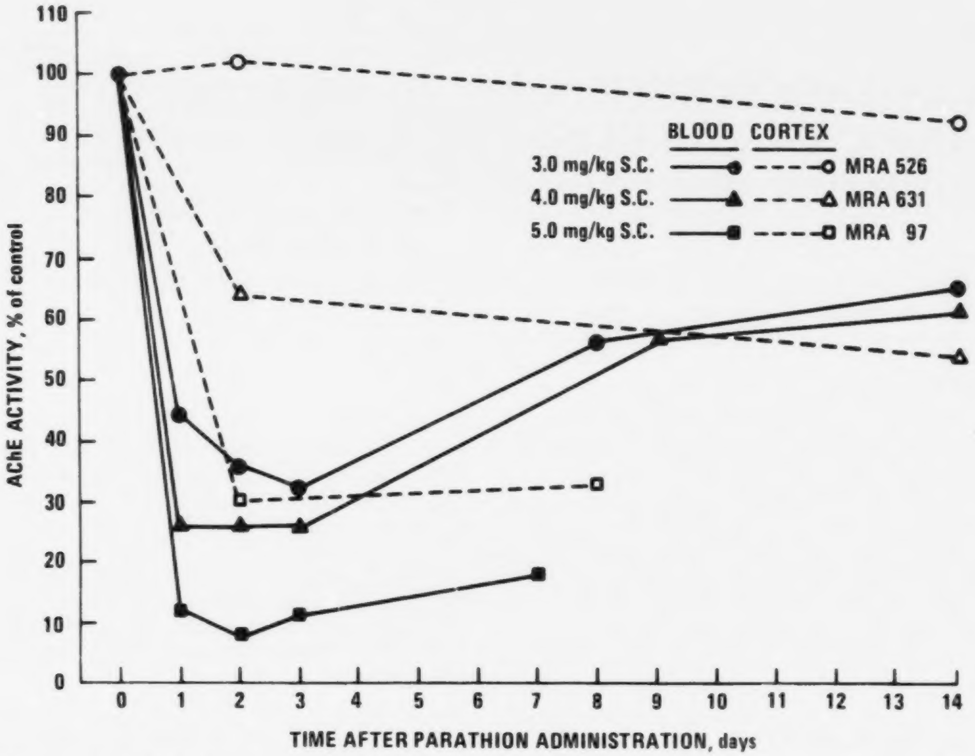

Fig. 6. Blood and brain AChE activity after parathion administration in three monkeys. Each animal was its own control. AChE activity in blood was inhibited to a much greater extent than it was in biopsies of parietal cortex in each monkey. Blood AChE activity showed some recovery during the study, whereas cortex AChE activity did not.

AChE activity in the CNS occurred after parathion administration in rats and monkeys. Development of tolerance to a number of AChE inhibitors has been reviewed recently (Bignami et al. 1975). Usually, an AChE inhibitor is administered and cholinergic symptoms are immediately evident, but despite continued AChE inhibition, the symptoms soon disappear. The major present hypotheses regarding the mechanism of onset of tolerance to AChE inhibition (Bignami et al. 1975), Woolley 1976) are as follows: (1) acetylcholine (ACh) levels, which become elevated immediately after AChE inhibition, become lower with time despite the persisting depression of AChE activity; (2) prolonged exposure to elevated ACh levels brings about a reduction in receptor sensitivity, thus counteracting the effects of AChE inhibition and allowing a recovery of function; and (3) the activity of other neurophysiological systems, either agonistic or antagonistic, alters to counteract the overstimulation of cholinergic systems.

Some evidence may be presented for or against each of these hypotheses, and still other possibilities remain to be explored. AChE and the ACh receptor must share some structural similarities because both combine with ACh. Paraoxon also combines with AChE at the active esteratic site and probably also has the structural requirements to react with the ACh receptor. It is possible that paraoxon first reacts with AChE to inhibit it and permit a buildup of ACh, resulting in cholinergic symptoms. After some delay, paraoxon next may combine with the ACh receptor and in this way reduce receptor sensitivity to elevated ACh levels and permit a return to more normal functioning, even though AChE is still inhibited. Recent progress in the isolation of the ACh receptor may soon make it possible to determine if paraoxon does indeed react with it.

Still another explanation has been provided recently by the observation that synaptosomes prepared from rats shortly after injection of a single dose of paraoxon showed significantly increased release and synthesis of ACh. However, when a slightly smaller dose of paraoxon was injected once daily for 5 days for an even greater total injection, the rate of synaptosomal synthesis and release of ACh did not differ from controls even though AChE activity was strongly inhibited in the treated animals (Speth et al. 1975). The interpretation appears to be that paraoxon initially acts on synaptosomes to increase ACh release and synthesis, thus causing cholinergic symptoms, but that the synaptosomes adapt to this effect. It remains to be seen how this possible explanation for the development of tolerance is related to other hypotheses presented above.

CNV AND SEP IN SHOE INDUSTRY WORKERS WITH NEUROPATHY RESULTING FROM TOXIC EFFECT OF ADHESIVE SOLVENTS[1]

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The diagnostic utility of event-related potentials (ERPs) in assessing the effects of exposure to environmental toxicants is a question of practical interest (Seppäläinen, this volume). A closely related question is the comparative sensitivity of ERPs and other measures of central and peripheral nervous system function used in the diagnosis of nervous disorders. Whereas previous studies (Giuliano et al. 1965, Zappoli et al. 1966) have shown that routine EEG was of little help for an early diagnosis of inorganic mercury poisoning, EEG, EMG, and conduction velocity abnormalities were frequently observed in shoe industry workers exposed to adhesive solvents (Giuliano et al. 1967, 1974, 1975). The present study was undertaken to evaluate the sensitivity of the CNV and somatosensory evoked potential (SEP) to the neurotoxic effects of adhesive solvents in workers exhibiting clear electroneuromyographic signs of polyneuropathy and EEG signs of diffuse brain damage.

Methods

Sixteen patients (15 females; age 14-51, mean 30.9) with toxic polyneuropathy from long-term occupational exposure to industrial adhesive solvents were studied. The chemical composition of the solvent mixture was: n-hexane, 46.30%; 3-methylpentane, 38.12%; heptane, 8.44%; methyl cyclopentane, 2.25%; 2-methylpentane, 2.24%; toluene, 1.25%; benzene, 1.25% (gas chromatographic determination).

CNV was recorded in six patients, SEP in six patients, and both EPs in four additional patients. CNVs and SEPs were also examined in 10 normal volunteers (students and researchers: 7 females; age 16-46, mean 28.7).

All patients exhibited hyporeflexia; asthenia, often associated with a clear motor deficit; more or less severe paresthesias and hypoesthesias; headaches; dizziness; and moderate psychic disturbances. Four subjects had moderate anemia and liver function impairment. All showed EEG abnormalities indicative of diffuse brain damage (prevalent slowing of EEG rhythms). Electroneuromyographic examination in all patients indicated signs of denervation associated with decreased nerve conduction velocity. The maximal motor conduction velocity (MMCV) was considerably reduced in all patients. The maximal sensory conduction velocity (MSCV) was in the lower normal range or borderline in 10 patients; in 6, a more severe decrement was detected. EEG and electroneuromyographic data were within normal limits in all control subjects.

A standard S1 (click)-S2 (50-dB intermittent tone burst terminated by button pressing) paradigm was used to elicit the CNV. Eighty to 100 trials with fixed 1.0- or 1.5-sec interstimulus interval (ISI) and variable 10- to 60-sec intertrial interval (ITI) were presented. EEG was recorded at F3, F4, C3, C4, and Cz with a 6-sec time constant. In all subjects, electrodes were referred to ipsilateral mastoids (Cz to linked earlobes) during the first part of the experiment, and to

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[2] G. Giuliano is associated with the Institute of Occupational Medicine, the other authors with the Institute of Nervous and Mental Diseases.

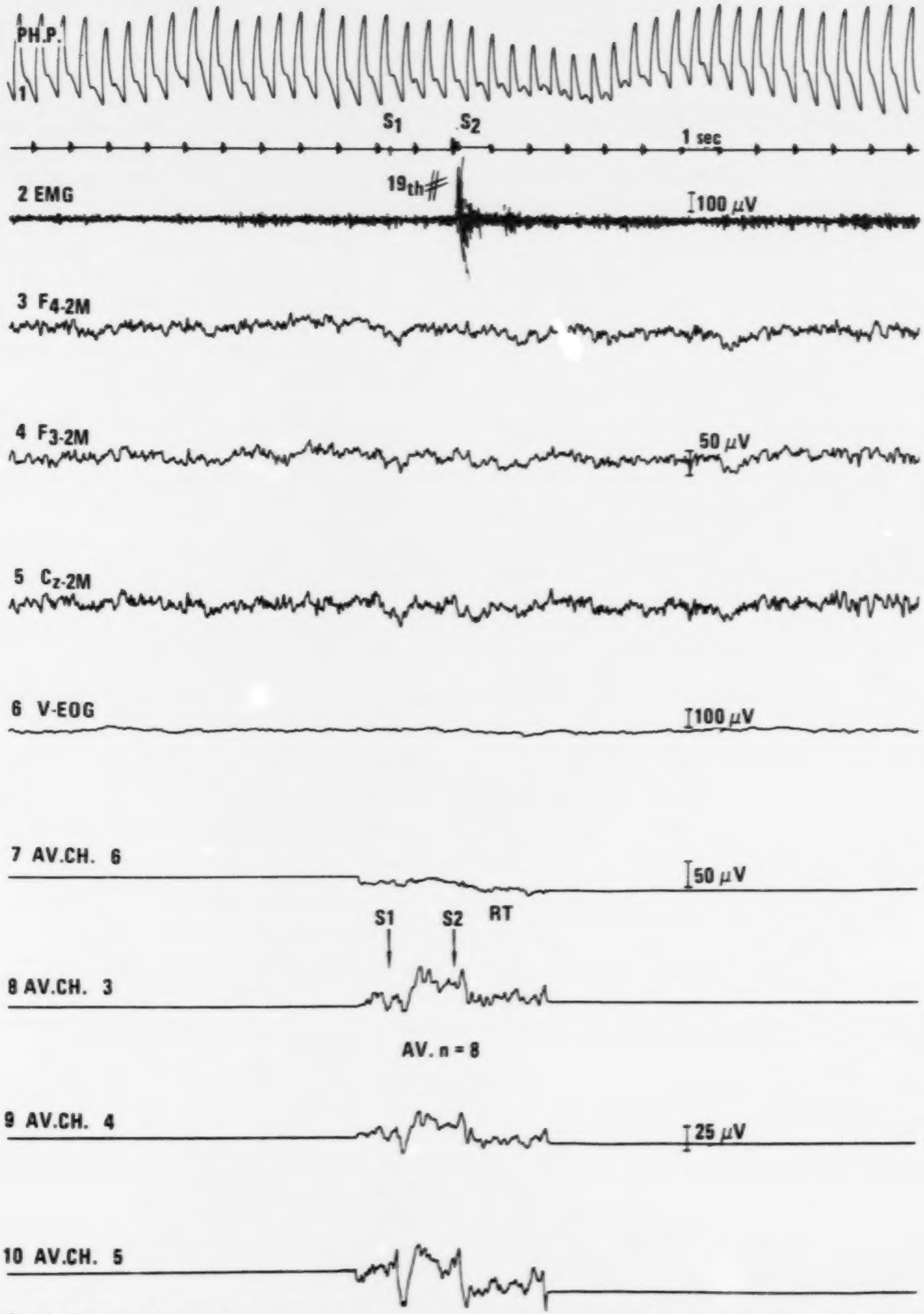


Fig. 1. Typical data records for patient. Female, aged 32, with severe industrial-solvent polyneuropathy, diffuse muscular atrophy and clear EEG and electroneuromyographic abnormalities: excessive diffuse theta waves; more marked MMCV (MN 39.3 m/sec; normal 57.65 ± 6.72 – LPN practically inexcitable) and less severe MSCV (MN 52.2 m/sec; normal 63.59 ± 4.04) decrement. Patient unable to walk when examined. From top: (1) fingertip photoplethysmogram. Signal and time marker: S1 (click) – 1.5 sec – S2 (imperative tone); (2) electromyogram of acting muscles; (3), (4), and (5) EEG recordings; (6) left V-EOG; (7), (8), (9) and (10) on-line averages of eight consecutive artifact-free trials of channels as indicated. 800-msec prestimulus analysis. TC = 6 sec. At 19th trial, RT to S2 c. 150 msec; mean RT of eight trials: 214 msec. Normal vasomotor response to trial.

linked mastoids during the second part. The first type of montage has proved useful for stable demonstration of possible hemispheric CNV asymmetries (Zappoli 1978). Vertical EOG, finger photoplethysmogram, EMG of responding muscles, stimuli, and reaction time (RT) were also recorded.

Averaging of EEG and V-EOG over trials was obtained by a signal analyzer with a four-channel input. For monitoring purposes, this signal analyzer was modified by connecting it to four of the polygraph channels to provide on-line averaging on primary records. Additionally, polygraph data were stored on analog FM tapes for off-line computer analysis.

Sets of 8 or 16 artifact-free trials were averaged in 5-sec epochs. CNV was measured as the mean amplitude of a 100- or 200-msec epoch preceding S2 relative to an 800-msec pre-S1 baseline.

SEPs were elicited by rectangular electrical shock of 100-μsec duration, delivered transcutaneously over the median nerve (MN) at the wrist for upper limb and over the lateral popliteal nerve (LPN) at the head of the fibula for lower limb. Stimulating electrodes consisted of silver discs with the cathode placed 3 cm proximal to the anode. Stimulus intensity was liminal for a weak muscular twitch. ISIs were irregular, 4 to 6 sec. SEPs were recorded through needle electrodes in the somatosensory area contralateral to stimulation and referred to linked earlobes.

The bandpass of EMG amplifiers was 15 Hz to 1 kHz or 10 kHz. Output was summated by a Neuroaverager (model 1172) triggered by the stimulator. The Neuroaverager offers the possibility of selecting the epochs to be averaged and rejecting the ones that are contaminated by artifacts. A single epoch is displayed about 3 sec, during which the operator may decide whether to load it into the summation memory. If not, the epoch will be automatically erased. An analysis time of 200 msec was used.

The SEP data were stored on analog FM tapes for further off-line analysis. SEPs were averaged over 50 or 100 artifact-free responses. Peak latencies and peak-to-peak amplitudes of successive components were measured.

The significance of differences in CNV, SEP, and RT measures between patients and controls was evaluated by the Student's t-test.

Results

In all 10 patients, it was very easy to elicit CNVs over all areas explored with what may be considered normal characteristics (Fig. 1) or characteristics very similar to those elicited from control subjects of comparable age range. For patients, CNV latency with respect to S1 (start of the negative deflection relative to baseline) ranged from 362 to 407 msec, mean 378; for control subjects, the range was from 358 to 413,

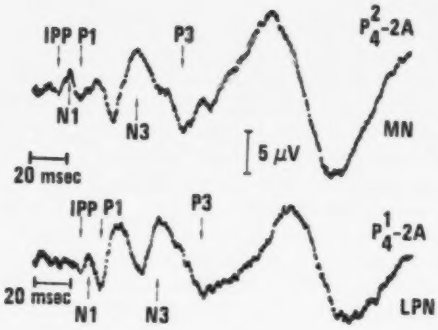
Table 1. Latencies and Amplitudes (±SD) of SEP Components for Contralateral Stimulation of Median and Lateral Popliteal Nerves (MN and LPN)

	Peak or component	Normal subjects (N=10)		Patients (N=10)	
		MN	LPN	MN	LPN
Peak latency, msec	IPP	14.66(±1.66)[a]	25.0(±4.18)[a]	14.55(±1.59)[a]	26.0(±2.76)[b]
	N1	19.5 (±1.35)	30.9(±3.21)	19.9 (±1.35)	31.0(±2.0)
	P1	24.4 (±3.23)	36.8(±3.55)	25.4 (±2.95)	36.8(±3.64)
	N3	57.2 (±3.48)	64.4(±5.14)	56.4 (±4.55)	64.2(±4.24)
	P3	77.4 (±6.98)	86.8(±11.36)	80.6 (±5.97)	86.8(±6.34)
Amplitude (peak to peak), μV	IPP-N1	2.96 (±1.11)[a]	2.04(±0.56)[a]	3.33 (±1.56)[a]	2.81(±0.74)[b]
	N1-P1	4.4 (±1.36)	2.57(±0.82)	5.0 (±2.92)	3.83(±2.23)
	N3-P3	7.05 (±1.62)	7.97(±3.9)	9.68 (±3.03)	9.2 (±5.33)

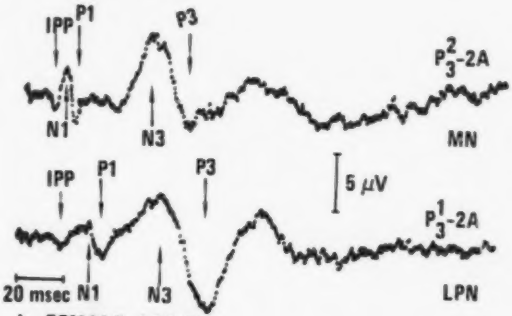
[a] Measures for nine subjects; IPP absent in one.

[b] Measures for six patients; IPP absent in four.

mean 372; the difference was not statistically significant. Amplitude, form, total duration of CNVs, and CNV resolution were normal, allowing for typical individual variability (the difference in CNV amplitude and duration between patients and controls was not significant). These CNVs were without clear and constant asymmetries in the various derivations utilized. In many of these patients, we observed surprisingly low RT to S2 (Fig. 1). The mean RT for all operant responses of the 10 patients was 212.4 msec (range 106 to 315); the corresponding value for controls was 198.7 msec (range 118 to 348). The differences between patients and controls were not significant. In two cases with rather severe polyneuropathy,

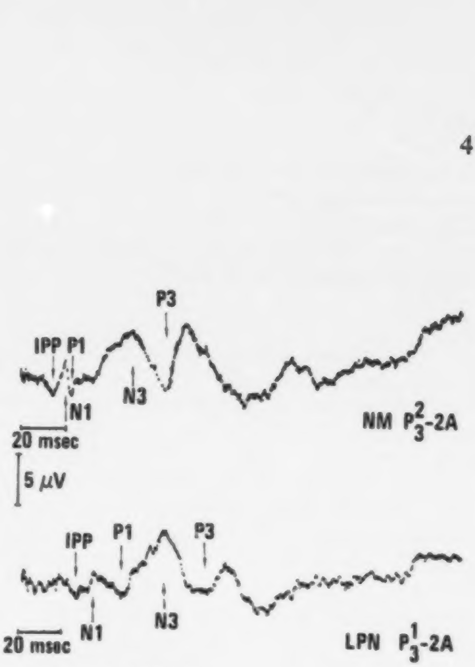


a. MALE, AGE 27

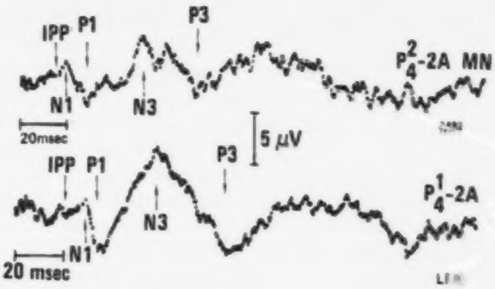


b. FEMALE, AGE 22

Fig. 2. Typical SEP in normal subjects to contralateral stimulation of MN and LPN (average of 100 artifact-free responses). Only consistent early and late deflections of the SEP are labeled. Positivity downward. P_4^2 or P_3^2, needle electrode fixed over the postcentral MN focus contralateral to stimulation: about 7 cm from the midline and 2 cm behind the coronal interaural plane. P_4^1 or P_3^1, LPN contralateral scalp focus: approximately 5 to 10 mm from midline and 2 cm posterior to the vertex.



a FEMALE, AGE 32



b. FEMALE, AGE 14

Fig. 3. SEP in patients with most severe toxic polyneuropathies. a. Female, age 32 (same patient as Fig. 1). SEP to MN contralateral stimulation, peak latencies in msec: IPP, 15.1; N1, 21.2 (at upper limits of normal range); P1, 24.2; N3, 52.1; P3, 70.2 (both at lower limits of normal range). SEP to LPN stimulation: IPP, 25.9; N1, 34.2 (at upper limits of normal range); P1, 45.2 (borderline for a little longer latency); N3, 64.8; P3, 83.2. All amplitudes of the three components measured in normal range values. b. Female, age 14. Worked at home with adhesive solvents without precautions. Severe polyneuropathy. Excessive diffuse slowing of EEG rhythms. MMCV at the Mn 46.9 m/sec (normal 57.65 ± 6.72) and at the LPN 32.7 (normal 53.9 ± 4.68). MSCV at the MN impossible to measure as NAP at elbow was practically indistinguishable from noise. SEP to MN stimulation: IPP, 17.3; N1, 21.4; P1, 29.9 (all at upper limits of normal range); N3, 53.1; P3, 74.9 (both at lower limits of normal range). SEP to LPN stimulation: IPP, 22.3; N1, 32.4; P1, 35.7; N3, 60.8; P3, 92.1. Amplitudes of SEP components were all within normal range.

RT ranging from 275 to 315 msec was observed. Fairly normal vasomotor responses to trials were present in all patients (Fig. 1). These results were obtained also in the cases that showed the greatest EEG abnormalities (marked slowing of EEG).

Table 1 shows latencies and amplitudes for early and late components of SEPs to MN and LPN contralateral stimulation in normal subjects and patients. Fig. 2 shows typical SEPs obtained in normal subjects. A small initial positive potential (IPP), extremely variable in amplitude, was found in nine subjects to precede the N1 component both to MN and LPN stimulation with a mean latency, respectively, of 14.66 ± 1.66 and 25.0 ± 4.18. In order of appearance, the more consistent early and late deflections observed with MN and LPN stimulation were: N1, P1, N3, P3.

IPPs were absent in one patient with MN and in four with LPN contralateral stimulations. Relative to normal subjects, none of the patients showed clear differences in latency or amplitude of components measured (Table 1). None of the small latency and amplitude differences observed between patients and controls reached significance ($p > .2$) Patients with the most severe toxic polyneuropathies and the greatest decrement of both MMCV and MSCV at the electroneuromyographic examinations (Fig. 3) were found to have, at the maximum, latencies of some components at the upper limits of the normal range of values measured in control subjects.

Discussion

CNV and SEP patterns observed in patients with toxic polyneuropathy and EEG signs of brain damage resulting from industrial adhesive solvents were within normal limits relative to control subjects. These results, therefore, lead us to express a negative judgment concerning the clinical usefulness of CNV and SEP measures for early diagnosis, especially at a subclinical stage, of toxic effects of these solvents on central and peripheral nervous system function.

When the significance generally attributed to CNV activity is considered it may be assumed on the basis of CNV data that these patients were not affected by important disturbances of arousal-vigilance mechanisms, attentional capacities, or information processing and cognitive functions. No other specific diagnostic tools were used to disprove the possible existence of minimal disturbances of such complex functions. During clinical evaluation, however, we never observed a real impairment of these psychic parameters.

As expected, neither SEP measure supplied any useful data for diagnostic purposes. It is well known that clear changes in SEP components (i.e., longer latencies and decreased amplitude) are observable in different types of polyneuropathy that are accompanied by severe impairment of the peripheral sensory pathways, marked MSCV decrement, damage of the dorsal column system (Giblin 1964, Bergamini et al. 1965, Halliday 1967). On the other hand, the toxic polyneuropathies resulting from adhesive solvents are generally characterized by a marked decrement of the MMCV and a much smaller decrease of the MSCV, without clear neurological signs of dorsal column damage. We also observed cases with marked decrement of the MMCV and with MSCV within the normal range or borderline. In these forms of polyneuropathy, therefore, for early diagnosis (at times even at a subclinical stage), evaluation, and longitudinal follow-up study, we consider electroneuromyographic measures still useful, especially MMCV. MSCV and EMG signs of muscular impairment are considered much less useful. Our present results, however, do not exclude the possibility that, in other forms of environmental toxicant central and peripheral neuropathy, particularly if the afferent pathways are severely damaged, studies of scalp-recorded evoked potentials may be a helpful diagnostic technique.

ELECTROENCEPHALOGRAPHIC ANALYSIS OF SUBACUTE EFFECTS OF METHYL-PARATHION IN THE MOUSE

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Neurotoxic symptoms induced by large doses of anticholinesterase-type pesticides have been correlated with biochemical alterations, consisting of a reduction in cholinesterase activity and consequent increase in brain acetylcholine levels (Bignami et al. 1975). However, there is no clear evidence of correlation between any long-lasting biochemical effect of single small doses of these drugs and behavioral impairment. It is also difficult to show the biochemical effects of small chronic doses until a state of severe intoxication is reached. In view of the importance of the cholinergic systems in electrogenesis, recording of brain electrical activity has been used as a sensitive parameter to show discrete alterations of the functional state of the brain induced by organophosphate pesticides (Loizzo and Longo, 1977). Electroencephalographic (EEG) changes demonstrate central effects more clearly than peripheral effects of drugs. Visual examination of EEG records yields qualitative, descriptive results; however, time series analysis, using power spectral techniques, allows quantitative evaluation of spontaneous nonparoxismal cerebral electrical activity.

In previous experiments using these methods, a dose-related effect on hippocampal EEG of the rabbit was described for Δ^6-*trans*- tetrahydrocannabinol (THC) (Willinsky et al. 1975). The minimal effective dose of THC (50 μg/kg iv) was equivalent to the threshold dose for psychic effects in man (Isbell et al. 1967). Using laboratory minicomputers, the method was improved to demonstrate the depressant effects induced by an anticholinesterase-type pesticide, methyl-parathion, on the hippocampus of the rabbit at doses as low as 0.05 to 0.1 mg/kg im (Loizzo et al. 1976). During these experiments no gross behavioral changes were observed in the animals.

A few studies have been undertaken to determine the minimal toxic levels of parathion and related compounds using electrophysiological methods. Santolucito and Morrison (1971) recorded the electrocorticogram from anaesthetized monkeys which had been receiving 0.3 mg/kg/day *per os* of parathion for 18 months. These authors found a reduction in both high-voltage slow waves and low-voltage fast waves, as well as increased synchrony between hemispheres. No significant alterations were found in monkeys fed 0.1 mg/kg/day of parathion. Dési (1973) reported a significant increase in electrical brain activity in rats fed for several weeks a diet containing bromophos in doses as low as 100 ppm (equivalent to 10 mg/kg/day; LD50 for bromophos is about 1650 mg/kg po). After 40 days treatment, this dose also induced a significant decrease in blood cholinesterase. Finally, Revzin (1973) found a dose-related decrement in septo-hippocampal evoked responses in monkeys challenged with single doses of mevinphos, ranging from 0.05 to 0.20 mg/kg im. No peripheral signs of poisoning were seen at these doses.

Investigations were initiated in our laboratories to contribute to the establishment of threshold limit values for substances acting on the central nervous system, and also to explore ways to detect, at the earliest possible moment in biological time, changes occurring in animal organisms from exposure to toxic substances in the environment.

Methods

Thirty DBA/2 male mice weighing 22 to 24 grams were chronically implanted with four cortical electrodes (anterior and posterior sensorimotor

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TABLE 1
TREATMENT SCHEDULE

Test Group	No. of Animals	Days 1, 2	Days 3-5		Day 6
Control I	4	Water	40 μl po	Water	Water
Control II	4	Sesame Oil	40 μl po	Sesame Oil	Sesame Oil
Exposure I	4		0.125	mg/kg methyl-parathion administered po in solution with sesame oil (total volume) $\leq$ 40 μl	
Exposure II	3		0.25		
Exposure III	3		0.5		
Exposure IV	4		1.0		
Exposure V	4 (3)		2.0		
Exposure VI	4 (3)		4.0		

cortex). The mice were randomly assigned to control and experimental groups as indicated in Table 1. The testing cycle consisted of six consecutive daily sessions with all mice receiving control treatments of distilled water or sesame oil on days 1 and 2, experimental groups receiving treatments of methyl-parathion as shown in Table 1 on days 3-5, and all mice receiving control treatments on day 6.

During each daily session, 120-sec epochs of EEG were recorded at 30 min intervals for two hours before treatment and again at 30, 60, 120 and 240 mins after treatment. Ninety dB intermittent noise was presented during recording epochs to arouse animals. EEG signals, bandpass filtered between 0.5 and 40 Hz, were recorded on analog tape for off-line computer (PDP-12) analysis. Sampling frequency was 128 Hz over 8-sec epochs. Using standard Fast Fourier Transforms, power spectra, ranging from 0 to 63.5 Hz with 0.5-Hz discrimination, were constructed and stored on digital tape. On the basis of a preliminary correlation analysis between frequencies (for methods, see Loizzo et al. 1978, Zapponi et al. 1978), six frequency bands were chosen: 0.5 to 3.5, 4 to 7, 7.5 to 12, 12.5 to 16, 16.5 to 20, and 20.5 to 40 Hz. Mean power in the frequency bands was evaluated during 2-min time samples (corresponding to 12 to 16 consecutive artifact-free power spectra). Mean values, representative of pretreatment, solvent-treatment, or drug-treatment states, were compared using two-way analysis of variance and the Duncan test (Senter 1965). Differences among dosage, time effects, and animals were evaluated. Absolute values and normalized values (the latter computed as a ratio of treatment to pretreatment mean values in each animal) were used to reduce inter-animal variability.

Results

Mice treated with water, solvent, and lower doses of methyl-parathion (0.125, 0.25, 0.5, and 1.0 mg/kg) resumed normal exploratory behavior in the cage after a few minutes of immobility following intubation. Mice given larger doses showed more evident changes in gross behavior (long-lasting hypomobility, piloerection, sometimes lacrimation). An inversion of the weight increment curve was also observed at the end of treatment. Two animals out of eight died the third day of treatment, one showing a cerebral abscess in the right posterior sensorimotor cortex.

On visual inspection, EEG records appeared normal in control animals and in animals given 0.125 to 1.0 mg/kg (cf. Loizzo 1969). In animals treated with 2.0 and 4.0 mg/kg, the records sometimes appeared slower in frequency, although the amplitude and morphology of waves appeared unchanged. No seizures were ever seen.

Computer analysis showed that the smallest dose of methy-parathion (0.125 mg/kg) induced a short-duration enhancement of power in two bands of the spectrum (7.5 to 12 and 20.5 to 40 Hz). This enhancement, however, was not significant. Doses of 0.25, 0.5, and 1.0 mg/kg showed a biphasic effect; i.e., these doses induced an enhancement of power in the 7.5 to 12 Hz range during the first 1 to 3 hr after administration followed by a depression of power in the same frequency band lasting up to 24 hours. The administration of the second dose of the drug, after a brief inconsistent enhancement of power in the same part of the spectrum, accentuated the trend towards depression. Fig. 1 shows the effect of 0.25 and 0.5 mg/kg of methyl-parathion on the 7.5 to 12 Hz frequency band of the spectrum in three animals. Administration of 0.25 mg/kg produced a significant depression in the mean frequency of the spectrum (cf. Hjorth 1975) during the first hour after treatment [control mean = 11.65 Hz, treatment mean = 10.93 Hz; 2-way ANOVA:F(1,11) = 11.89, $p < .01$]. A linear regression analysis of the cumulative effect of

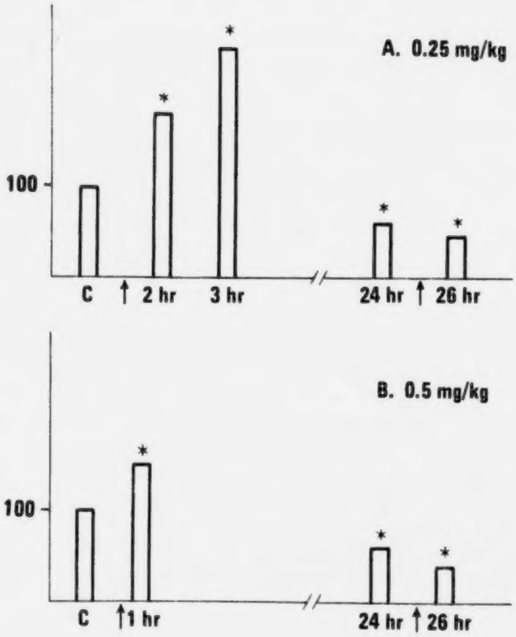

Fig. 1. Temporal effect of two doses of methyl-parathion on power in the 7.5 to 12-Hz range of EEG in mice. Power is normalized with respect to predrug control. Asterisks indicate significant effect ($p < 0.05$) relative to control.

0.5 mg/kg methyl-parathion 24 hrs after treatment on three consecutive days indicated an increasing depression in the absolute power of 4-7 Hz EEG activity (Table 2). Note also the high within-subject variability. Higher doses (2.0 and 4.0 mg/kg) induced a constant depression in several frequency bands. Both total power and the mean frequency power values were reduced. These effects, which started 1 to 2 hours after the first drug dose, lasted as long as 24 hours, and in general became more marked after successive treatment (Table 3).

Discussion

Pryor et al. (1966) and Ebel et al. (1973) have shown that different inbred strains of mice may have different cholinesterase levels in various parts of the brain. However, preliminary work in our laboratory (unpublished) showed that the LD 50 of methyl-parathion in DBA/2 male mice was 39 mg/kg po. These results were consistent with Wills (1970), and indicated that DBA/2 mice were not particularly sensitive to the drug, at least with respect to acute toxicity. However, since data obtained from inbred strains may be unreliable, further data are needed. EEG effects induced by the vehicle of drug administration should also be considered.

Our results indicate that methyl-parathion in mice induces EEG modifications which can be detected and quantified at doses as low as 0.25 to 0.5 mg/kg po (approximately 1 to 2% of LD50). These modifications consist primarily of an enhancement of power at 7.5 to 12 Hz, and are followed by long-lasting depression in the same frequency band. For low doses, behavioral effects are minimal. Larger doses (2 to 4 mg/kg, corresponding to 5 to 15% of LD50) generally produce more dramatic effects (long-lasting depression) on EEG rhythms and clear changes in gross behavior.

These effects have been observed by Dési (1973) in rats administered bromophos chronically (50 mg/kg/day po) and by Vajda et al. (1975) in the EEG of rats given a single dose of parathion (3.5 mg/kg po) and recorded 7 days after treatment. Dési also reported a decrease in brain and blood cholinesterase and conditioned responses of animals after several days of

TABLE 2
Regression analysis of effects on absolute power of 4-7 Hz EEG induced by 0.5 mg/kg methyl-parathion 24 hours after successive treatments.

	SS	df	MS	F
Subjects	8.214.004	2	4.107.002	55.69*
Linear Regression	898.837	1	898.837	12.19*
Deviation from Regr.	170.267	1	170.267	2.31 (n.s.)
Error	2.286.164	31	73.747	
Total	11.569.272	35		

Coefficient values: a = 1260.2; b = −190.6; Sb = ± 54.6
*p < .001

TABLE 3
Effects on EEG power, expressed as percent of control values, induced by 2 mg/kg methyl-parathion 1 hour and 24 hours after dose II.

	Frequency Bands (Hz)						
	0.5-3.5	4-7	7.5-12	12.5-16	16.5-20	20.5-40	Total Power
1 hr after Dose II	92	87**	105	82**	88**	97	89*
24 hr after Dose II	54**	74**	49**	52**	51**	52**	56**

* $p < .05$
** $p < .01$

chronic treatment. Others (Bignami and Gatti 1967 for parathion, Kaloyanova-Simeonova 1961 for chlorthion, Medved et al. 1964 and Russel et al. 1961 for Systox,[1] Lewis et al. 1973 for mevinphos) have reported changes induced by very low doses of anticholinesterase-type pesticides on conditioned behavior in animals.

Rider et al. (1969) failed to confirm either biochemical or clinical deficits in men treated orally for several weeks with 19 mg/*toto*/day po of methyl-parathion. Note that this dose, administered to a man weighing 70 kg, is equivalent to 0.25 mg/kg, the effective threshold dose used in our experiments.

Several authors (see reviews by G. Clark 1971; Bignami et al. 1975; Mertens et al 1975; Woolley, this volume) observed that cholinergic symptoms appear immediately following administration of an acetylcholinesterase inhibitor. Despite continued cholinesterase inhibition, the behavioral and/or clinical symptoms soon disappear. The results of Warburton and Segal (1971) and Dési (1973), however, indicate that tolerance to anticholinesterase effects may not occur for certain conditioned behaviors. Low doses, moreover, can produce clear signs of poisoning under particular dietary conditions (Casterline et al. 1969). The question remains which behavioral deficits occur at low doses that do not produce somatic signs of poisoning.

Conclusion

Organophosphate pesticides vary so widely in systemic distribution, in affinity for different types of cholinesterase, and in metabolism that findings with one agent in one species cannot be generalized to other pesticides in the group or to other animal species. However, parallel studies on the electrophysiological, biochemical, and psychological (or clinical) effects of these drugs on laboratory animals or men are rare. Metcalf and Holmes (1969) conclude that long-term exposure to organophosphorus compounds can induce irreversible or very slowly reversible brain disfunction.

Our results show that it is possible, using interdisciplinary techniques for the simultaneous investigation of several physiological, biochemical, and psychological parameters, to evaluate threshold effects of these drugs on brain function in laboratory animals. Multivariate statistical procedures, such as discriminant analysis or factor analysis (Loizzo et al. 1978, Zapponi et al. 1978) may also help in determining the most sensitive and cost-effective neurobehavioral parameters for future research on the neurotoxicity of pesticides and other chemical hazards in the environment.

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[1] Diethyl-0-(ethylthioethyl) phosphorothioate 2:1 with diethyl-S-(ethylthioethyl) phosphorothioate.

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VIII. SCALP DISTRIBUTION

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USE OF SCALP DISTRIBUTION AS A DEPENDENT VARIABLE IN EVENT-RELATED POTENTIAL STUDIES: EXCERPTS OF PRECONFERENCE CORRESPONDENCE

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This paper presents excerpts from preconference correspondence related to the use of scalp distribution as a variable in ERP studies. The following people contributed to this correspondence:

1. R. Cooper, Burden Neurological Institute, Bristol, England.
2. L. Deecke, University of Ulm, Germany.
3. W.J. Freeman, University of California, Berkeley.
4. W.R. Goff, Veterans Administration Hospital, West Haven, Connecticut.
5. T.W. Picton, University of Ottawa, Ontario, Canada.
6. W. Ritter, Herbert H. Lehman College, Bronx, New York.
7. D. Ruchkin, University of Maryland School of Medicine, Baltimore.
8. P. Tueting, Psychiatric Institute, New York, New York.

The province of this discussion is the complex of technological, analytic, and interpretational problems encountered whenever two or more recording channels are used in an ERP experiment. The utilization of multiple channels affirms a faith in their nonredundancy. That is, the investigator assumes the data recorded from multiple channels will provide more information than he could gain from recording any of these channels alone. The investigator expects that, at least on some occasions, systematic differences will appear in the recordings obtained at different electrode sites. The interest in multiple recordings, or scalp distribution (SD), is essentially an interest in the differences between simultaneously recorded evoked responses. The differences must be systematic in order to be interesting; that is, they ought not to be attributable to the random fluctuations that can be expected whenever any measurement process is applied to any biological phenomena. In addition to the criterion for systematicity, it is also necessary that the differences, recognized as intracranial, be useful in resolving some of the questions that motivated the recording of the ERP. Data become information only if the data resolve some uncertainties. The implication of this last statement is that there must be some relationship between the SD and the independent variables manipulated or monitored by the investigator.

The above assertions imply that for the successful utilization of SD data, there will be at least the following: (1) some reasonable rule for which the experimental hypothesis would dictate the placement of the recording electrodes; (2) procedures for measuring the differences between the waveforms recorded at different sites; (3) techniques for assessing the reliability of such differences (that is, answers to such questions as: Is a given difference significantly different from zero? How reliable is this particular estimate of the difference between two specific electrodes?); (4) techniques for reporting SD data in a way that would communicate to the reader both the central tendencies and the variabilities of the data; (5) finally, when an appropriate picture of the scalp distribution has been obtained, procedures that will allow relating it to the experimental variables so as to obtain answers to the experimental questions that motivated the SD recording.

There appear to be two distinct, but closely related, rationales for the use of SD. Both assume that the potentials that can be recorded from the scalp represent the activity of neural structures located inside the cranium. Because different structures have different patterns of activity at different times and because those structures are diversely located inside the cranium, the potentials that can be recorded at any point on the scalp at any time are quite likely to be different from potentials recorded at other sites. The differences between scalp locations will presumably reflect differences in the activity patterns of the intracranial sources. This is the central dogma shared by all ERP investigators, and it is this central dogma that underlies the recording of SDs.

There are two discernible trends in the use of SD data. Crudely put, one can record SD data to make specific inferences about the intracranial location and activity pattern of neural generators. In this case, SD becomes somewhat of a substitute for the stereotactically placed electrode, which one cannot readily use with humans. The other approach, while assuming a relationship between intracranial generators and SDs, is focussed on establishing that different SDs are associated with different values of some independent experimental variable. The differences are used as auxiliary variables in dissociating the effects that experimental variables have on different evoked response components. Such an analysis depends strongly on the assumption that the differences in SDs are physiologically meaningful, though the specific form of the physiological relationship need not be known.

As in any classification, there is much that is arbitrary, and no doubt the trends and attitudes are well mixed in most of our different investigations. The distinction, however, is valid, at least in the sense that the investigator's primary interest strongly dictates the nature of his data acquisition process and the manner in which he will assess the data. Those interested in making inferences from SDs to intracranial sources have tended to focus on "standard," normative, experimental arrangements in which stimuli are presented under conditions which are as neutral as possible; the primary interest has been mostly taxonomic, and the problems of measurement and statistical inference, therefore, have not been crucial. In most cases, many subjects are run in a few fairly simple experimental conditions, the experiment being so designed as to minimize the between- and within-subject variability. By averaging over subjects, an apparently standardized picture is obtained. The intellectual challenge in this approach is most often in developing rules of inference from the SD to the intracranial generators.

Investigators who try to use scalp distribution as an auxiliary variable in dissociating the effects of experimental variables can ignore with relative impunity the intracranial generators. (Some even get away with so obvious a solecism as reporting recordings "from Wernicke's area" when referring to the scalp location where they happen to have attached their electrode.) On the other hand, the measurement problem in this context is considerably more severe. When the investigator's main claim is that the SD observed under condition A is different than that observed under condition B but not different than that observed under condition C he presumably has a technique for assessing the degree of difference between SDs and has assured himself that the difference between A and B is a "real" difference and, what is considerably more difficult, has convinced himself that there is no difference between conditions A and C.

The previous paragraphs outline the main issues with which a discussion of SDs is most likely to be concerned, and in fact the correspondence conducted in preparation for the EPIC IV conference touched in a variety of ways on all the issues enumerated above. I shall use this framework to present excerpts from the correspondence. It will become immediately obvious that the correspondence is inchoate. Many issues have been very briefly touched upon. Others, even though debated in some detail in the correspondence and at the Congress are still far from resolution. Nevertheless, a remarkable consensus did emerge on a number of the issues. That this is the case is best revealed through a perusal of the several papers included in this section. They were written after the conference and represent a synthesis of the writers' views prior to the meeting, as reflected in their contribution to the correspondence, coupled with the effects of the discussions at the conference. The following pages represent: (1) excerpts of precirculated correspondence, primarily concerning issues not covered in postconference contributions; (2) comments made by Cooper at Kanuga and the response elicited from Allison; (3) papers contributed by Picton, Ritter, Goff, Freeman and their associates.

Preconference correspondence

Problem definition

Donchin: Two major questions arise and form the substance of this group's assignment. The first is largely a methodological question and relates to the manner in which the patterns of spatiotemporal variations ought to be measured. The problems involved are the proper placements of the electrodes, the manner in which the information from different electrodes can be combined, the most economical and effective way of expressing the patterns, the most efficient and useful ways of communicating results, and the most appropriate statistical procedures for comparing patterns obtained on different occasions.

The second question, very substantive and difficult in nature, has to do with inferences that might be drawn about intraskull events from variations in the scalp distribution of the potentials. What is the nature of the inferences that might be drawn legitimately from variations in the amplitude distribution of the potentials over the head? If lateral asymmetry is demonstrated, can one infer differential activity of the hemispheres? If some component is always larger in the parietal leads, what can be inferred concerning the origin of this component? If the scalp distribution of visual or auditory potentials is different, can we indeed infer that either was generated in the primary cortex? What should one make of the fact that CNVs tend to show differential distributions in the anterior-posterior axis?

However we answer this set of questions, even if the inferences we can draw about internal brain events from scalp distributions are minimal, the fact that behavioral variables can consistently manipulate scalp distribution is of interest. I hope that in our discussions the utility of such variations can be easily assessed.

Electrode placements

Ruchkin: Correlation between ERPs recorded simultaneously at different scalp locations bears upon the question of the position and number of recording sites to obtain a complete description of ERP distribution upon the scalp. I believe that a quantitative answer to this question can be developed. The ERP amplitudes may be viewed as a function of three parameters: time and the two spatial dimensions that define location upon the scalp.

It is well known that in order to obtain a complete description of a waveform as a function of time, it must be sampled at a rate at least twice the highest frequency of the waveform (in the time domain). The same principle applies in the spatial domain. The location of electrodes along a line in space should be such that the average distance between electrodes is about one-half the length corresponding to the highest spatial frequency of the ERPs. The concepts and mathematics are the same as used for signals as a function of time. Instead of dealing with a graph of a waveform plotted with time as the independent variable (obtained at a single point on the scalp), we deal with a graph of a waveform plotted with distance along the scalp as the independent variable (obtained at a single instant of time). From an abstract point of view, the problems of characterizing these two waveforms are conceptually and mathematically the same.

I suggest that, as part of the attack upon the problem of how to optimize recording of scalp distributions, information be obtained concerning the spatial frequency spectra—in the same manner that temporal frequency spectra are obtained. I do not suggest that electrodes then be (blindly) placed at "mathematically optimum" sites on the scalp. Certainly as much use as possible should be made of underlying anatomy and physiology. However, analysis of ERP spatial frequencies would provide us with a statement of the maximum degree of resolution possible and consequently with an indication of the number and spacing of electrodes required for a complete description of the distribution of ERPs over the scalp.

Freeman: Assuming one can identify and isolate an event, one can then ask: where is it located, what is its spatial extent, and what is its spatial function (variation with distance in the intensity and/or time of onset)? Further, what is its maximal rate of change with distance, and, if it is periodic (in space), what is its maximal spatial frequency? If it is an event in a neural surface such as cortex, is the spatial frequency the same in all directions, or is it a plane wave (the difference between a tray of pebbles and a sheet of rods, a grating or an interference pattern)? As Ruchkin states, the spatial interval between adjacent electrodes in an array must in theory be less than half the wavelength (one/spatial frequency). In practice, due to noise from various sources, it would be better to have eight or ten electrodes/wavelength rather than two or three, where the wavelength is not known or is imprecisely known, and the electrode array should extend over the distance of at least four or five cycles if a periodic variation exists.

Cooper: Differential amplifiers appear to be necessary since high in-phase (common mode) rejection is necessary. Thus, all recordings are bipolar in the sense that the measurement is the difference between one electrode and a reference point, which usually has to be on the head, primarily because of the EKG. Even if the EKG is balanced out, the noncephalic electrode can still be influenced by activity from the base of the brain just as an electrode on the foot still picks up the EKG (using the leg as a conductor). If the electrical field to be measured is small, say confined to the occipital region, then common reference is good, but if the field is large, the common reference can inject signal. To decide which type of recording method to use, the field distribution must be known; but this is what is to be determined.

Just as EKG can be recorded from hand and foot, so EEG activity, perhaps even alpha activity, can be picked up from, say, the tip of the nose. Murphy's law will ensure that the worst case will obtain, and it must be assumed that the reference is active to a greater or lesser extent. This makes interpretation very difficult.

After many years of trying I have come to the conclusion that there is no way of avoiding this problem; the problem can be minimized, but the magnitude of the minimum distortion *cannot* be determined.

Deecke: A basic assumption of all potential mapping on the scalp is that a homogeneous dielectric layer covers the potential generators. However, the skull varies in thickness. Since bone has the highest resistance of all the layers between cortical surface and scalp electrode, differences in skull thickness can result in amplitude differences. There are only few data in the literature, but it has been shown that a slightly thicker skull can cause a marked attenuation, e.g., of the alpha rhythm. We measured the skull thickness of 51 skulls of an anatomical collection at our recording locations (C3, C4, P3, Pz, P4) and found that the lateral parietal skull bone was 20% thicker than the midparietal one. At the vertex, the skull is still thinner than midparietally (posterior margin of the former fontanella). It is quite certain that this factor contributes to the frequent vertex maximum of evoked potential components. Other factors are the massive accumulation of cortical tissue of both hemispheres, including mesial cortex in the depth of the sagittal fissure, the favorite locus for potential pickup in volume conduction. Using data available in the literature, we estimated a possible attenuation of 19.2% at P3 and P4 as compared to Pz for potentials in the alpha range.

Measurement of differences

Tueting: I have been looking at evoked potential waveforms from different sites on the head (monopolar with linked earlobe reference) long enough to be rather perplexed about what is really going on. For example, when identifying a component by shape, size, and approximate latency, the latency of the component may change systematically from electrode to electrode in a given plane. Two interpretations of this observation, however, seem possible: (1) the component actually does shift latency over the head; (2) the reciprocal masking of overlapped components having different topographical distribution may *appear* as a latency shift over the head.

At issue is whether it is physiologically or physically possible to conceive of a generator producing a component that varies slightly in latency from electrode to electrode in a given plane. What kind of generator would it be—a widely distributed cortical generator triggered at different latencies in separate areas? A discrete generator producing latency shifts because of its orientation to the surface? An alternative explanation that components from any given electrode site are overlapped and masking one another (and that we are simply seeing more or less of a given component at an electrode site depending upon the relative amplitude contribution of these masked components) can be tested. Presumably, experiments could be designed to either enhance or eliminate one of the components of the composite. Or, with a good hypothesis of the theoretical latencies of the components, could principal components analysis unravel the components?

The approach to this issue is important. I think it could affect the validity of measurements reported or used in principal component analysis. If N100 amplitude is considered and the computer is set to measure the most negative peak between 90 and 110 msec (at all electrode sites for all subjects for all conditions), the results will not be valid if there are actually two components, a slightly more frontal N105 and a slightly more parietal N92.

In view of the above, the decision of setting a latency search window, either for a human 1-mm-box counter or for a computer, should probably not be taken lightly.

Deecke: After the most admirable efforts of Freeman aiming towards (and coming very close to) a complete description of stimulus-dependent electrical events in a certain brain system, it is hard for the rest of us to continue evoked potential research in the old-fashioned way. However, let me enter here a plea for simplicity. I think that the human eye-brain system is still a very good apparatus for potential evaluation (with its superb ability to perceive invariances, Gestalwahrnehmung, etc.), with only one disadvantage: It is always the eye-brain system of the investigator that is biased. Since we were aware of this, we tried to force ourselves to "double-blind analysis" not only when comparing patients with normals, but also, for instance, in the evaluation of laterality differences. This should, in my opinion, be considered a general rule for scalp distribution research as well as preaverage editing and the use of a sufficient number of subjects ($N > 20$) because there are subject-specific differences.

Problems of statistical assessment

Donchin: To get the discussion rolling, I shall make a few provocative remarks. With few exceptions, we have all been treating the problem of scalp distribution much too simple-mindedly. What we normally do is measure the amplitude of components at different scalp loci, often using only two "homologous" scalp locations such as C3 and C4. Broad generalizations about laterality or the preponderance of parietal activity are then based on the relative amplitudes at two such electrode locations. This has been dictated by instrumental and analytic restrictions. However, the field is rapidly outgrowing its dependence on simple averagers as the use of sophisticated computing and data acquisition devices becomes widespread. Therefore, we ought to develop an approach to measurements of parameters of the distribution of the potential over the head that capitalizes on this increased data acquisition and computational power. The problems involved in the evaluation of distribution of a quantity in time, over a two-dimensional space, are often encountered in geography, meteorology, or field-potential analysis in physics. Should we not find out how these disciplines deal with the problems and try to emulate what is useful?

The statistical problems are formidable. To take but one example, if you compare potentials recorded simultaneously at different scalp locations you cannot, in all honesty, perform tests that assume that all measurements represent independent samplings. There is considerable correlation between different electrode sites, and these correlations ought to be taken into account in the description of the distribution. But there are serious problems of presentation. What is the best way to convey your ideas about a distribution? Do we need contour maps? Do we need conventions for presenting the data? Are plots of the type Remond (1968) published necessary?

Ritter: My inclination is, wherever possible, to use the simplest, most straightforward analysis and presentation. If, for example, an investigator merely wishes to establish asymmetry for a given class of events (e.g., monaural stimulation, unilateral motor activities, language stimuli), then the use of several judiciously placed pairs of electrodes may suffice. The demonstration of asymmetry is probably best accomplished by measuring components in the standard manner.

To conclude that two components do *not* have different distributions, however, it is not sufficient to record from only a few sites. An interesting illustration is provided by the negative wave elicited by a missing stimulus. We found this component larger centrally than parietally for both missing tones and flashes (Simson et al. 1976), as was found by Picton et al. (1974) for missing clicks. But as we reported at Brussels, the negative wave for missing flashes is different than that for missing tones in that the former has two foci, one near the vertex and a second, of even greater magnitude, on the lateral surface of the scalp near the border of the occipital lobe. This component, then, appears to be modality specific, and the only way we could have established that was by placing a fairly large number of electrodes across the scalp (13 in this instance).

Goff: I certainly agree that more sophisticated types of analyses should be tried to express topography data, but the fact that they are more sophisticated does not automatically mean that they are better for the particular purpose. With regard to correlations between different electrodes, a description of topography is essentially a description of correlations between electrode locations. The problem is that, so far, it has seemed practical to describe the correlations only for amplitude.

Responding now to Tueting, both of her interpretations as to the cause of shifts in component latency are probably applicable to most components most of the time. The reciprocal masking of overlapping components is probably the dominant cause of what appears to be shifting component latency. This certainly seems to be the case in our topography study. To cite but two examples where components are known to be masked by other components: (1) Under barbiturate anesthesia in man, the SER P45 wave drops out, revealing a large primary negativity. (2) The negative component of the somatic late response (SLR) is apparently masked in scalp recordings by the vertex potential. An actual example of two components of approximately the same latency is given in our somatic topography paper (Goff et al. 1977) where the frontally distributed P100 wave occurs about the same time as a parietally focussed P100 wave. We believe that the frontal component is extracranial, while the parietal component is the scalp reflection of the positivity of the SLR.

Donchin: The problem of using scalp distributions as dependent variables is not easily dismissable. When the differences are large, they may be easily observable even with a few electrodes. We detected laterality differences in the motor potential using two electrodes (Kutas and Donchin 1974). We can now evaluate P300 and slow wave distributions with three electrodes (Squires, K. et al. 1977). Fortunately, however, in these cases the differences were obvious. The issue, as Ritter points out, becomes more complex when one records from three electrodes and fails to find a difference. This is analogous to an earlier period of CNV research (Donchin 1973) when investigators felt that it was sufficient to record from the vertex. Even if no differences are found between vertex ERPs, it is possible that there are differences between frontal and parietal recordings, one or the other dominating in different experimental conditions. The vertex seems to be the pivot on which the frontal-parietal axis rotates. It is conceivable that the favored Fz-Cz-Pz axis may show no differences in distribution, while the distributions are in fact quite distinct lateral to the midline. The problem is common to "negative" results; if you find no differences you never know whether (1) the differences do not exist or (2) your measurements were taken in an inappropriate place, time, or manner.

Freeman: Donchin's point is well made regarding use of spatial distributions of potential either as variables dependent on time-varying sensory, motor, and central event states or as independent variables for localization of "sources" with respect to anatomical landmarks. However, in both cases, there is an underlying assumption that the neural event ("potential," slow wave, fast wave, "bump," peak, component, X-complex, ERP, SEP, etc.) is a unitary event (comparable to a single action potential assignable to one neuron at an unequivocable location), or that a complex is the sum of a set of such bumps. However, the CNV or P300 wave is probably not a unitary event, but consists rather of a set of similar events overlapping in time and space, each event having some characteristic waveform, and the weighted sum of their potential fields giving rise to one or more bumps at the scalp. Each member of the set of events might involve a substantial number of neurons, e.g., 10^4 to 10^7 comprising part of a population; and on each trial in a series of events, the fraction and/or location of that part of the population may shift, or it may shift with time during each trial of the event. So it is reasonable to try to ascertain that the maximal observable potential of a given sum of events is located in or over area 4, 7, or 17, although the underlying neural events remain undefined and therefore unlocalizable–volume conductor theory notwithstanding.

The chief problem lies in the empirical description or definition of a "bump" as a certain function of potential in time, as it is observed from a recording electrode near a field maximum. The oscillograph screen photograph or ink tracing gives us a certain gestalt, and we tend to "see" the same waveform in records from nearby points. This is the "bias" to which Deecke referred. This is especially true if the number of points is small (four or less) and the spectral distribution of the event is narrow, e.g., a "slow wave" or a "burst." If larger numbers of electrodes (e.g., 32 to 64) or recording sites for sequential observations (e.g., 100 to 500) are used, most such events (in my experience) change shape in a continuous manner with distance across the event, and the gestalt is submerged in variance. I think the success of Donchin et al. (1975) in differentiating P300 and CNV may be due in part to the small number (two or three) of electrodes used. For the same reason (that our mind's eye locks onto a simple waveform and induces us to see it again), we tend to decompose complex waveforms into a sequence of "bumps" and then spin our wheels trying to "localize the source" of each of them.

The analysis of principal components, in which one uses location in an observable complex as a stratifying variable to tease out the overlapping waveforms in a superimposed set of events, is one alternative way to decompose the complex. One of the two main difficulties is that each component in an overlapping set may have a waveform that is causally unrelated to its neighbors but is statistically related (in the sense that a somatosensory and an auditory evoked potential may be diphasic and have a nontrivial correlation coefficient, because they have similar mechanisms and waveforms and "look alike"). In this case, they cannot be separated by a linear model. The second difficulty is that neural mass events move in the tissue, but the electrodes are fixed. Factor analysis and related techniques cannot distinguish between variance due to changes in the location and intensity of activity. Each "factor" may be a peculiar *gemisch* that fails to give clear information about either the time-varying locations or time courses (time-dependent amplitude) of neural events.

Picton: I have been hoping that someone would provide a simple statistical approach to finding differences in scalp distribution. I do not feel competent to propose such a statistical technique, and I might be stepping where angels fear to tread since the more mathematically inclined members of the correspondence have been amazingly quiet in this respect.

Could one not apply the principal components analysis described by Donchin (1966), substituting a scalp location dimension for the time dimension? This could be done by selecting one, or a small number of time points and evaluating scalp distribution for these points. It might then be possible to determine significant differences in scalp distribution at these selected latencies using procedures described in the first part of Donchin's paper and to describe the scalp distribution differences using the technique of principal components analysis described in the second part of that paper. However, it becomes quite difficult to arbitrarily preselect one or several latencies, and it would be nice to analyze the data over both latency and scalp distribution.

Having raised the possibility of multivariate analysis, I feel bound also to express my reservations concerning these techniques. I must admit that if the access to such data crunching devices were easier and if my understanding were deeper, perhaps I might be less cautious. Generally, if the effect one is demonstrating is large, this can be statistically proven using fairly simple statistical techniques rather than the more powerful multivariate analyses. My general approach has, therefore, been to create the largest possible effect and to use the simplest possible statistical tests.

Distortion of signals in signal enhancement techniques

Cooper: Averaging is a poor method of recording evoked potentials. This is particularly so in multichannel recording, since it is very easy to assume that if signals from two brain regions, say Cz and Fpz, change together in the average, then they change together in the individual trials. This need not be so, as the spatial distribution might change during the collection of the average–and this is what we are trying to measure.

More attempts must be made to extract data from individual trials by correlation or pattern-recognition techniques or, better still, by designing experiments that give large amplitude responses that can be seen in the original record. From some recent work in Bristol (Weinberg and Cooper 1972, Weinberg and Papakostopoulos 1975), I believe this can be done. Averaging techniques, demanding artificial repetition of the event, as they do, set an experimental framework that is at variance with the realities of the external world where "one trial learning" is common.

Inaccuracies in the measurement of data

Cooper: There has been discussion on the use of statistics in our work, and I agree with both Donchin and Picton: Donchin for his desire to improve reliability in the face of variability and Picton for wishing to avoid using them by looking for "sore thumb effects." Both are right, of course, but we must NOT use statistics like a drunk and a lamp post; we must use them for illumination, not for support. We must use them, as it were, to *reduce* the variability rather than improve the constant factor. Let us use them to design better experiments by showing where the source of variability lies so that we can reduce it by changes of paradigm or recording conditions.

Freeman: The definition of the components in an empirical event and their localization to sets of neurons requires a deep knowledge of the structure and dynamics of the region in which the event occurs, to the extent that the locations, patterns of spread, and time courses can be predicted for particular components. This view is set forth in detail in *Mass Action in the Nervous System* (Freeman 1975). It is, to be sure, a long way from the olfactory bulb to the association neocortex, but I will maintain that unless you develop and use a theoretical basis for predicting waveforms from local neural anatomy, topology, and dynamics, you will be wallowing in principal components indefinitely. Of course, one of the best, if not *the* best, sources of ideas in the development of predictions is the result of component analysis, so my challenge is not directed toward its use as a means, but toward its being regarded as an end.

Picton has brought into better focus my view of one of the roots of the difficulties we face in the analysis of ERPs recorded at the scalp and presented a possible way to deal with the difficulty directly. The sense of confusion and uncertainty stems from the lack of clear-cut templates (engrams, gestalts, archetypal patterns) of what the components of such events "ought" to look like.

I perceive now an area of neglect in these studies, and a positive approach to this difficulty. It begins with the careful and painstaking parametric testing of a specific event in a small number of individuals. That is, a stimulus-bound event should be established in a set of well-defined and fixed circumstances, and the stimulus intensity (or perhaps some other of its parameters) should be varied in small steps from threshold on prolonged averaging to a supramaximal level at which the form of the event is fixed for further increase. At each step, an adequate number of events should be taken to determine (initially) the intrinsic variability for fixed experimental conditions. Thereafter, at each step, if sensory stimulation is being used, the event should be studied with pairs of stimuli to determine the superposition characteristics of the response. If at some step or over a small range of steps the event or a significant part of it displays the superposition property, and if the input is a linear function such as a pulse, step, or sine wave, then the event (or that part of it) can be described as the sum of a set of linear functions (exponentials, damped sine waves, etc.). That is, there is a clear-cut expectation of what the components "ought" to look like.

At this point, the task is to fit a curve to the event waveform, i.e., the number of components, their types, and the approximate values of their parameters must be determined by graphic techniques. The Fourier transform of the event by numerical integration is often useful here. When a curve has been fitted to one response from one individual at one step, it becomes a template for a set of responses at that step. (An average of the set is often optimal as the basis for the first template.) The uncontrolled variation takes two forms. If the same equation can be fitted to every response, the variation is expressed in the continuous distributions of the parameters. If some of the responses can only be fitted by the addition or deletion of other basis functions (i.e., using a different equation), then there are one or more discontinuous changes in the event.

The procedure of fitting is extended to responses over a range of steps and over a class of individuals. The variation again occurs either by variation in the parameters or by differences in the set of basis functions. The result is the emergence of a set of response templates for a specific set of experimental conditions. These will give the basis for describing in detail the number and kinds of intrinsic variation, the types and properties of the "noise," the degree of complexity of the responding system (in terms of the number and kinds of basis functions), and the dimensions of the variance space; they will also provide a basis for research and classification of individual responses that were averaged to provide the data base for analysis.

The linear response domain may be quite small, but my experience has shown that it can be extended quite broadly by piece-wise linearization. Further, in each curve-fitting procedure there are residuals, which often provide crucial insights into ways to restructure the templates. One should also expect to be sent back to the experiment to redefine the conditions so as to assist in the emergence of acceptable templates. In my experience, I have not really "seen" an evoked response clearly until I have tried to fit a curve to it. The difference between my intuitive expectation expressed as an analytic function and what actually has been recorded, when plotted in the same coordinates, has impressed me with how faulty the intuitions can be.

One may suppose that this procedure may not be appropriate for the complicated and seemingly highly nonlinear and time-varying scalp-recorded responses to sensory input. However, my students and I have begun with quite similarly appearing evoked potentials from the prepyriform cortex, olfactory bulb, hippocampus, superior colliculus, and cerebellum, and in each case we have found and extended a linear domain. The neocortex and its sensory pathways are unquestionably more complex, but I believe that the stepwise procedures for pattern development are feasible and should be explored. Certainly this is one systematic and well-defined way out of a morass of loosely structured empirical data. It does not require *a priori* knowledge of the dynamics of the responding systems, and in fact gives information about the dynamics that animal experimenters may not have, may crucially need, and may not be able to get from animals.

Spatial analysis enters in two ways. At the outset, the collection of events from multiple sites helps to determine the choice of a particular location for intensive analysis, because it is simpler in form, reproducible across individuals, or optimally conforms to the superposition principle. Later, when one has a template, one can use it to determine the amplitude and latency distributions at the surface and begin to explore the overlapping of two or more events, perhaps initially fused into one template. As I have written earlier, one must have a template as a time function before one can determine a spatial distribution.

In summary, there is a systematic way of developing clear-cut expectations of what an event "ought" to look like. It begins with parametric and paired-stimulus testing, and proceeds through curve-fitting and the study of the variations of the parameters. At each stage, it refers back to the experimental situation for modification and verification. Properly used, it can provide a rigorous basis for deciding what is signal and what is noise. That problem is probably the major obstacle in applying multivariate statistical analysis directly to the digitized data. Finally, it does not depend on the development of dynamic models of cortex, and indeed may materially assist in the formulation of such models by animal experimentalists.

Picton: Freeman's excellent comments consider the problem of noise. He suggests "supramaximal" averaging in order to determine any spatial distribution function. This is most applicable to the analysis of the relatively constant responses such as the auditory brainstem potentials or the early somatosensory components. The later evoked potential components will, I believe, be highly refractive to such a systematic analysis since, as Freeman points out, they are "highly nonlinear and time-varying." Even such constant responses as the auditory brainstem potentials have been reported to vary over prolonged periods of time (e.g., Amadeo and Shagass 1973). The problem of obtaining the template waveform is especially relevant to the very late components, such as the P3, which are highly affected by inevitably changing perceptual attitudes even under fairly rigidly defined circumstances. If one accepts relatively noisy data as inevitable, how big are the problems involved? If, instead of the supramaximally averaged template waveform, one uses a relatively noisy waveform such as the vertex record, how bad is any derived spatial function?

This complete derivation of the spatial function of the waveform is probably most needed when one is extrapolating to underlying generators. Perhaps a simpler and immediately more important problem is to compare the spatial distributions of a component under two different conditions to see whether they are indeed significantly different. If so, one can then state with some degree of certainty that they must be differently generated. This in itself, even without the knowledge of the underlying generators, is an important conclusion. What then is the most appropriate analysis, and how does one compensate for the different amplitudes under the two conditions?

Freeman: The curve-fitting approach, which I suggested earlier and Picton commented on, is particularly applicable to highly variable late components of ERPs. The method requires two stages. In the first stage, a large set of ERPs is averaged to remove as much of the noise as possible, while removing the variability of the ERPs as well. A curve is fitted to the supramaximal average that constitutes a matched filter. This same curve is then fitted to each ERP in the set or to subaverages of them by allowing the parameters in the equation to vary; i.e., the filter is now adaptive. The fits are not as close as the superaverage, but they should not be, because noise is present in the subaverages. The end result is that the variance in the set of ERPs is expressed in the matrix of coefficients of the fitted curves.

One way of looking at the procedure is to assume that the ERP is an information carrier that is modulated on each trial and is also obscured by background EEG. Supramaximal averaging permits us to specify the form of the carrier, which is the same across trials (e.g., it is always a sinusoidal burst or a step), but the details change on each trial (its frequency, amplitude, delay, rise time, decay time, etc.). The superimposed EEG obscures the signal, but the equation gives an expected generic form in the search for the signal. The curve-fitting procedure gives a "best estimate" of the particular form of each signal while separating it from the "noise," i.e., the residuals (Freeman 1975, ch. 7).

Goff: Using dipole analysis and attempting to establish the location of sources by application of field potential theory is irresistible. But among the problems is one aptly put by Freeman, namely, that we tend to decompose a complex waveform into a sequence of bumps and then try to locate each one. However, I do not know how else to begin. The problem can be approached in two ways. One way, the one that Vaughan and others use, is to make assumptions about the location of the source and then see if the empirical data seem to fit. The inverse method is to attempt to determine from the empirical data where the source is, *assuming*, and this is the crux of the matter, that there is a single equivalent dipole generator. In some cases (e.g., postcentral gyrus primary activity), this is probably a valid assumption, but in most cases we simply do not know. I agree with Picton that the Henderson et al. (1975) paper is excellent, particularly because of the elegant *in vitro* simulations of dipole sources. We have been using a very similar technique in collaboration with Sidman.

We now use a three-sphere model, which takes into account the different resistivities of brain, skull, and scalp, and find that it gives good agreement with data where the location is known in advance. This method, like the Henderson et al. (1975) technique, is based on the Wilson-Bayley equation (Wilson and Bayley 1950), although we use a different algorithm and think our method is more stable in some situations. But the big question is, do you trust the answer the computer gives you? There is no objective way of determining this, but you do get a number that amounts to a goodness-of-fit measure and at least gives some assurance that the observed topography is consistent with the assumption of an equivalent dipole located where the method says it is. We are now using this technique on some of the depth electrode data, but whether it will help us understand this complex set of data remains to be seen. In any case, these techniques are important and are worth pursuing.

Distortion of signals from brain to scalp

Cooper: No measurement represents the true value of a parameter since the measuring instrument distorts the signal. However, this is not a major problem, as the accuracy we desire is only a few percent. Our problem arises because we are forced to work at a distance from the source of the signals and do not know the transmission characteristics of the tissue in between. Nor do we know the shape and amplitude of the sources of the signal.

The one thing that we do know is that we are dealing with *a system that obeys fundamental chemical and physical laws* and that these laws are inviolate in the sense that they must not be used when the data fit into them and ignored when the data do not fit. *They are there for all time and all conditions of the experiment.*

If there is a paradox (and there are many), then the data collection and assumptions made during the interpretation of the data must be critically examined since something must be wrong. For example, consider acoustic responses that apparently come from deep structures by some kind of volume conduction. How can these data be reconciled with the lack of volume conduction that makes Freeman and ourselves use electrodes with spacing of a few millimeters? Or how can the interpretation of the AEP over the central fissure as a dipole be reconciled with work showing that the so-called phase reversal is not quite 180° but is a time shift and that one of the components can be selectively blocked by certain maneuvers? Let us be clear that when we talk about a dipole we are stuck with a dipole and that it must always show the characteristics of a dipole, such as the rapid attenuation of the field with distance. Why do cortical electrodes on the surface of the frontal lobe just above the eye show no sign of the blink artifact that is such a nuisance on the scalp immediately above these cortical electrodes? Or why can some large amplitude cortical activity not be seen on the scalp immediately above the area of cortex involved? Scientific discovery is often made by people realizing that data and theory do not fit—let us be rigorous in our approach to this problem and perhaps we too can discover more about why and how we pick up EEG signals.

In 1965, we in Bristol published our ideas about scalp/cortex relationships, declaring that there is virtually no volume conduction in the brain tissue and that scalp activity is only obtained when a relatively large area of cortex immediately below the scalp electrode is involved in synchronous activity (Cooper et al. 1965). We still believe in these concepts, since they are the only ones that we can think of that explain our data. Yet they are not satisfactory to explain the data presented by Vaughan and Ritter (1970) on the sources of the auditory responses or to explain the presence of the auditory brainstem potentials on the scalp, both of which depend on a great deal of volume conduction. Or can the paradox be resolved in another way? Because we pick up the EKG in the foot, we do not think that the heart is in the leg. Could it be that we are using the structures of the brain (ventricles?) as conductors to the source of the potential?

Detailed measurement of potentials might give us the answer but would it not be better to measure the direction of flow of current since this is what we are after—the localization of the changes in ionic currents? And what sort of attenuation do we get from artificial generators that are implanted in the brain? And how do the various types of tissue and fluid between scalp and cortex attenuate eye blink potentials?

Only when these basic questions can be answered will we be able to extrapolate the scalp data into cortical localization with more certainty.

Donchin: I should explain in more detail my distinction between the use of scalp distribution as a dependent variable and its use for source localization. Consider for example our work on the lateralization of the motor potential. We were interested in the degree to which lateral asymmetry will vary with the hand used by the subject. As it happens, it does (Kutas and Donchin 1974). It is perfectly reasonable to conclude from the nature of these asymmetries that the readiness potential is large over the hemisphere contralateral to the responding hand, and from our general knowledge of the motor control system, to infer that the readiness potential may have something to do with activity in the motor cortex. Note, however, that we would be hard pressed to provide convincing evidence that the potentials we record *indeed come from the motor cortex*. This is a speculative inference that is, and this is the main point, not truly necessary for the main purpose of the experiment, which was to determine if there is a relationship between the responding hand and scalp distribution. This is relevant for such questions as the degree to which this "readiness" activity represents nothing but generalized arousal (which ought not to be differentially distributed among the hemispheres). The lateral asymmetry of the readiness potential differentiates it quite nicely from the CNV. Thus, the scalp distribution in this case is used merely as a dependent variable, allowing us to choose among competing hypotheses.

Similar use of the scalp distribution appears in such tasks as those described by Simson et al. (1977), which allow differentiation between N100 and N190. Or the demonstration in the paper by Donchin et al. (1975) that the CNV and P300 have quite different scalp distributions. In the latter paper, we again make no inferences about the localization of the source of either the CNV or P300. All we are interested in finding out is whether the two have the same or different scalp distributions. We feel of course that different scalp distributions imply different sources and therefore that the two components are different. Whether or not the mechanisms for inferring the specific source are available, the fact that the two are different is sufficient to make them useful dependent variables.

PROBLEMS IN USING VOLUME CONDUCTION THEORY TO LOCALIZE EVOKED-POTENTIAL GENERATORS

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One of the most important reasons for measuring scalp distribution of evoked potentials is to determine the brain regions that generate the potentials, for this information is required to formulate theories of brain function.

The basic mechanism underlying the EEG is the movement of an electrical charge (ions) across the semipermeable membranes of neurons in the cerebral cortex. This ionic movement gives rise to current flow in the external medium and to potential differences that can be measured with voltage amplifiers. The voltage measured, EEG or EP, depends upon the distribution of current, which in turn depends upon the relative impedances of the infinite number of current paths available. Location of cerebral sources is only possible if the distribution of current (or voltage) is known in three dimensions. Inferences of location based on scalp distribution are dependent upon assumptions of the impedances of various tissues through which the current flows. Little relevant quantitative work has been done, and most theories are based on potential distributions determined from intracranial electrodes in man and animals (e.g., Cooper et al. 1965). The main finding of this work was rapid attenuation with distance from the apparent generator, a common finding, exemplified by the high spatial frequencies referred to by Freeman and Gerbrandt in this volume. Attenuation is probably due to the relatively high impedence of tissue (mainly membranes) compared with the low impedance of extracellular fluid. In effect, the generator is surrounded with an insulator that restricts the field to the immediate extracellular space. Measurement of tissue and fluid impedance at EEG frequencies is difficult because electrodes themselves have high impedances caused by electrical double layers.

Volume conduction in brain tissue appears, therefore, to be very small indeed. For this reason, I consider the dipole models originally suggested by Brazier (1950) and more recently by Henderson et al. (1975), and others to be inappropriate. Nevertheless an explanation is needed for the apparent far-field effects described by Jewett (1970 a, b) and others, in which brain stem potentials are recorded at the vertex (referred to ear lobes, which seems to me a rather inappropriate reference for auditory potentials). Another factor noted in intracranial EEG recording is the absence of blink or eye-rolling artifact, even when subdural electrodes are located very close to the eyes. Recently I used averaging techniques triggered by scalp blink potentials to measure intracranial blink amplitude. Fig. 1 shows that blink artifact is attenuated by a factor of about 30 between an electrode near Fpz and a subdural electrode immediately below. This suggests, however, that we should never record EEG using scalp electrodes since the electrocorticogram is not 30 times bigger. Cooper et al. (1965) speculated why EEG can be seen in scalp recordings: only when areas of cortex are engaged in synchronous activity does the attenuation *apparently* become smaller. The high attenuation of blink potentials must be due to the three-dimensional current flow caused by closure of the eye (probably changing the current paths) with preferential paths leading to apparent electrical screening of subdural electrodes. These data show, however, that the brain cannot be assumed to be an isotropic medium with conductivity like that of saline—an assumption basic to dipole calculations.

Brain stem potentials are still unexplained, although the small amplitude suggests the far field of a dipole (see Allison, this volume). Another possibility which would be difficult to prove is that the field is recorded via the relatively low-resistance ventricular fluid system in the same way that EKG can be recorded from the foot and hand when, loosely speaking, the leg and arm are used as conductors tapping into the heart's potential field.

Measurement of the magnetic currents using magnetoencephalography, in which direction of current flow can be determined, may possibly throw some much needed light on this subject.

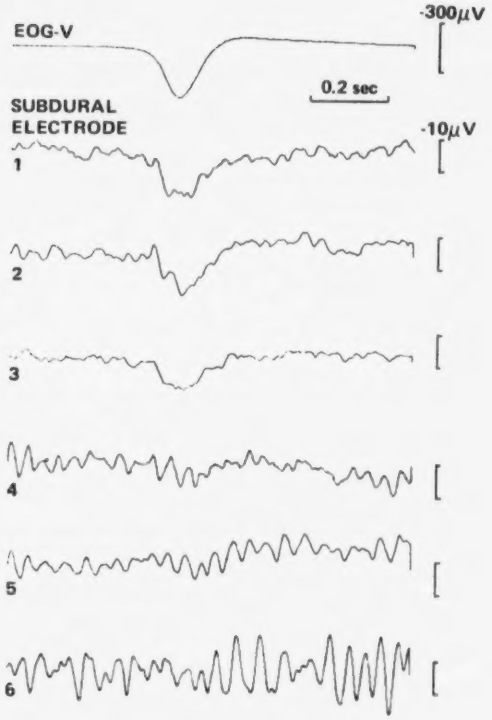

Fig. 1. Average blink potentials (N=96) from vertical oculogram (EOG-V) and six subdural electrodes referred to an average reference of 60 intracerebral electrodes in a psychiatric patient. The averager was triggered by the eye blink using a Bereitschaftspotential-type program that averaged activity before and after the blink. Subdural electrode 1 was immediately beneath the oculogram electrode, which was just above the right eyebrow. Electrodes 2 and 3 were 8 and 16 mm posterior to electrode 1 (near the right frontal pole). Electrode 4 was approximately beneath the midpoint between F4 and C4. Electrodes 5 and 6 were located 8 and 16 mm posterior to reach sensory motor cortex. Only the anterior electrodes (1, 2 and 3) show a blink potential with about a 30-fold attenuation.

CALCULATED AND EMPIRICAL EVOKED-POTENTIAL DISTRIBUTIONS IN HUMAN RECORDINGS

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Cooper raised the issue of volume conduction in evoked potential (EP) recording. He noted that under some conditions there is little apparent spread of field potentials in brain tissue. This conclusion derives mainly from recordings of spontaneous EEG activity in man and animals (reviewed by Cooper et al. 1965). Clearly, there are situations in which volume conduction appears minimal. Recording EPs from the cortex or deep structures, one observes very sharp attenuation of EP amplitude as the electrode is moved away from a focus. On the other hand, as Cooper noted, the fact that one can record brainstem evoked potentials from the scalp argues for an appreciable degree of volume conduction. I believe this apparent paradox can be understood if one takes into account the circumstances in which scalp recordings are made.

Consider the distribution of potentials generated by a dipole source located under a plane and oriented perpendicular to it. The potential recorded at the surface is given by

$$V = K \frac{PD}{(X^2 + D^2)^{3/2}}$$

where P is the potential of the dipole point source, D is the distance from the dipole to the surface, and X is the distance along the surface (Brazier 1949). Cortical dipole sources are usually superficial. Polarity inversion is typically seen at depths of 0.3-1.0 mm (e.g., Schlag 1973) and, in theory, potential distributions should be calculated for a D within this range. An EP generator is never, however, a point source, but is an area of tissue which, in the simplest case, lies in a plane. Such an extended source can be simulated by increasing D. For D equals 1 cm, the equation yields the potential distribution shown as a solid curve in Fig. 1. There is a rapid attenuation of amplitude with increasing distance. For example, 2 cm from the source the potential is less than 10% of its maximal value. If the source is moved nearer the surface, the peak is even steeper, while for deeper sources it is flatter. The region of rapid attenuation of amplitude near the source corresponds to the "near field" of Jewett and Williston (1971). As the distance from the source increases, amplitude approaches an asymptotically low level and is approximately a linear function of distance. This region corresponds to Jewett and Williston's "far field."

Under appropriate circumstances, the amplitude of human EP components can agree well with calculated values. The dashed curve in Fig. 1 is the amplitude of SEP component N55 (G.D. Goff et al. 1977) as recorded from the pial surface of a patient during localization of the central sulcus. An 8-electrode array spanned the median nerve representation area of the postcentral gyrus in a medial (electrode 1, to left of curve) to lateral (electrode 8, in right part of curve) direction. The SEP at electrode 5 is shown in the inset. N55 is the negativity at about 100 msec (it is increased in latency in most epileptic patients). N55 was chosen for this purpose because it is large, easily quantified, and (unlike shorter latency components) appears to be undistorted by other activity in the same latency range. Agreement between calculated and empirical amplitude is fairly good (and could be improved further by simulating a more extended source by increasing D slightly). Electrodes 1-7 are within the near field while electrode 8 is in the far field.

Now consider the comparable potential recorded from the scalp; it is illustrated in the inset as recorded from C4, where its scalp amplitude was largest. Its latency is earlier than that seen at the cortical surface, as is often the case in scalp-pial EP comparisons (Broughton 1969; Allison et al. 1977). The scalp-recorded potential is miniscule relative to its pial counterpart. The distance between C4 and the cortical surface is about 1.5 cm; the calculated amplitude for this distance is indicated by the shaded triangle on the curve. In addition to the effect of distance *per se*, there is a further order-of-magnitude decrease as a result of attenuation by dura, skull and scalp. The empirical amplitude is indicated by the unshaded triangle and corresponds to an apparent D of about 4.5 cm. Scalp topographies (G.D. Goff et al. 1977), together with other pial recordings (unpublished), indicate that N55 is generated in the crown of the postcentral gyrus. Thus its amplitude, as recorded from the scalp, is greater than if it were generated in sulcal cortex (Vaughan 1974). In other words, this component represents a "best case" situation for volume conduction to the scalp. Yet, if plotted on the same amplitude scale as the pial recordings, it would hardly be visible, although by scalp-recording standards it is a relatively large, highly reproducible component. Because the averaging technique is now commonplace, one may tend to forget how easy it is to record potentials quite distant in the far field. An extreme case is the brainstem auditory evoked potentials, which can be several hundred microvolts in amplitude in brainstem recordings in cats (Jewett 1970) but are usually less than a microvolt as recorded from the human scalp.

Thus, the question is not whether there is, or is not, volume conduction–we can say definitely that there is. Rather, the question is where the recording electrode is in relation to the source. If it is close to the source, i.e., in the near field, small differences in location have a large effect on amplitude, and one is inclined to believe there is little volume conduction. If one is recording at a distance, i.e., in the far field, and if the apparent distance is even greater as a result of interpolation of tissue of low conductivity, one is then likely to conclude that the head is a good conductor and that it does not much matter where the electrode is placed.

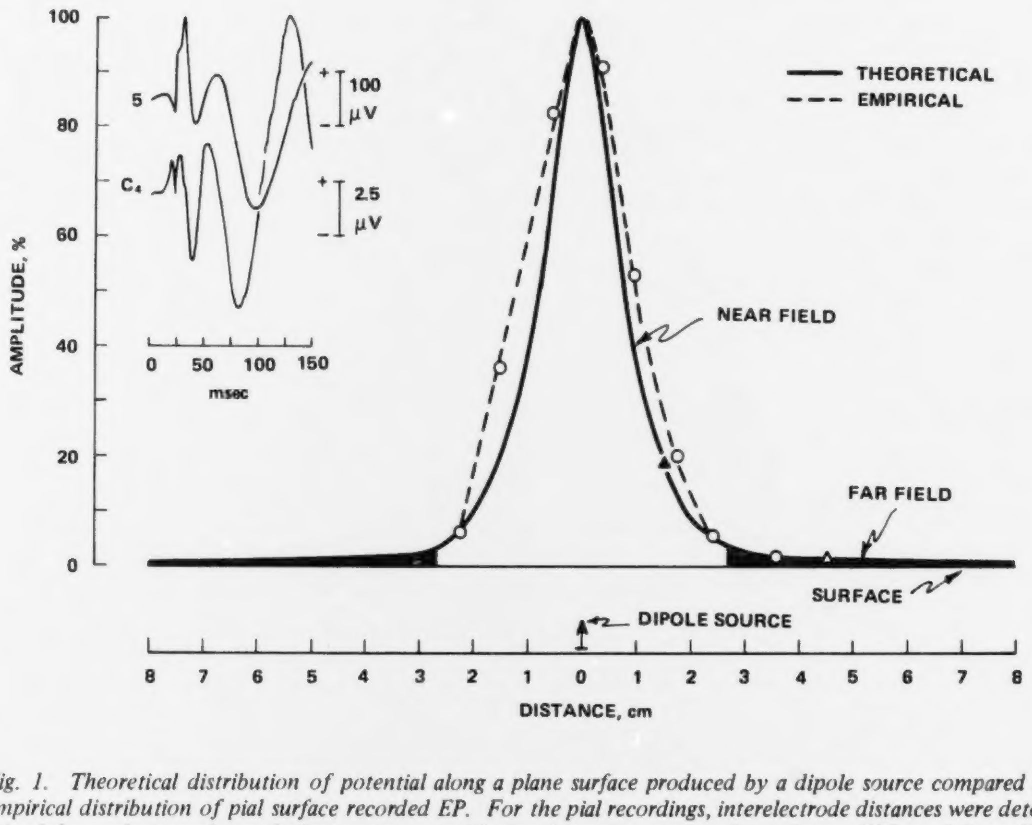

Fig. 1. Theoretical distribution of potential along a plane surface produced by a dipole source compared to empirical distribution of pial surface recorded EP. For the pial recordings, interelectrode distances were determined from photographs made during surgery, with the electrode array in place. Inset: SEPs to left median nerve stimulation recorded from pial surface of right postcentral gyrus (electrode 5) and scalp (C4). Scalp recording was preoperative. Details in text.

METHODOLOGY AND MEANING OF HUMAN EVOKED-POTENTIAL SCALP DISTRIBUTION STUDIES

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Scalp distribution studies of human event-related potentials involve the recording and evaluation of such waveforms at multiple scalp locations. Such studies provide information helpful in determining the possible generator sources of the scalp-recorded events and in comparing electrical events recorded under different physical or psychological conditions. This paper will attempt to describe and illustrate the techniques of recording and displaying scalp distribution data and the procedures and problems of their interpretation.

Recording

Electrode location

Most scalp distribution studies utilize the International Federation 10-20 system of electrode location (Jasper 1958). In this system, standard electrode sites are determined by dividing distances along the head into prespecified ratios. The use of ratio measurements makes the system more adaptable to different sizes and shapes of heads than systems based on absolute meaurements. Electrodes located outside of the standard 10-20 sites are often utilized in evoked potential research for two reasons. First, a greater spatial concentration of electrodes might be necessary to delineate small differences or asymmetries in scalp distribution. Vaughan (1974) suggested the minimum practical spacing of scalp electrodes should be approximately 2.5 cm. Jeffreys and Axford (1972) utilized 2.5-cm interelectrode distances in their evaluation of the visual evoked potential scalp distribution. Peronnet et al. (1974), in their studies of the auditory vertex potential, used a coronal chain of 13 electrodes rather than the 7 provided by the basic 10-20 system. Theoretically, at least two electrodes are needed in the spatial period of an evoked potential component (see Ruchkin's correspondence in Donchin, this section); unfortunately, the spatial frequency of most scalp-recorded components is unknown and cannot be calculated prior to mapping. A second reason for using nonstandard electrode locations is that the optimal recording sites for certain evoked potentials may lie outside the basic 10-20 system. Several researchers (e.g., Matsumiya et al. 1972; Brown et al. 1973; Megela and Teyler, this volume) have attempted to record meaningfulness-sensitive evoked potential components from electrodes overlying Wernicke's area between the temporal and parietal electrodes of the 10-20 system. The optimal recording location for the somatosensory evoked response elicited by peroneal nerve stimulation is a few centimeters posterior to the vertex (Tsumoto et al. 1972) and by median nerve stimulation a few centimeters behind the C3 or C4 electrodes (Calmes and Cracco 1971).

Fortunately the electrode labels used in the 10-20 system were developed so as to allow the incorporation of additional electrode locations. Fig. 1 represents a possible modification of the 10-20 system to provide for a greater concentration of electrodes on the scalp and for more accurate electrode location for specific purposes. The modification

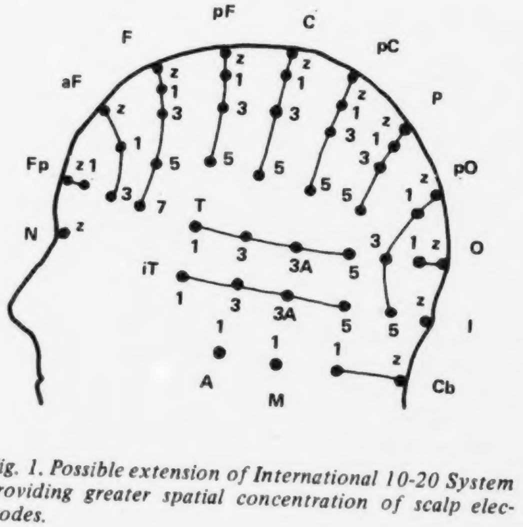

Fig. 1. Possible extension of International 10-20 System providing greater spatial concentration of scalp electrodes.

involves the addition of anterior frontal, posterior frontal, postcentral, preoccipital, and inferior temporal lines of electrodes. The only necessary numerical nonsequiturs are the T3a and T4a electrodes. The system is fairly simple in measurement, provides interelectrode distances of between 2 and 4 cm, and can be easily described. It should be noted that using more closely spaced electrodes need not provide any further meaningful information. Interindividual variability in brain topography may reduce the advantage gained by the closer spacing of the electrodes.

Recording montage

Because of the low amplitude of the evoked potential signal and the pervasiveness of environmental electrical noise, all ERP recordings are performed using differential amplifiers. As has often been pointed out (W.R. Goff et al. 1969, Cracco 1972, Vaughan 1974), it is usually preferable to record scalp activity relative to a distant indifferent electrode rather than between adjacent closely spaced electrodes. Closely spaced bipolar montages may occasionally be helpful. Polarity reversal might reveal a point of maximum amplitude or locate a fairly focal evoked potential component. Yet, even in such cases, referential montages can provide the same information. Bipolar recordings are particularly difficult to understand if multiple ERP components of similar latency are recorded at different electrodes.

Reference electrodes

The choice of an indifferent reference can be extremely difficult. There is probably no place on the human body on which an electrode will not pick up, through volume conduction, some electrical activity of the brain. Indeed, the indifference of many reference electrode locations is a matter of some difference of opinion. For example, Vaughan and Ritter (1970) considered the nose to be indifferent for the auditory vertex potential recording, and using a nasal reference demonstrated a phase reversal of the N1 and P2 components of the auditory ERP across the Sylvian fissure. They therefore suggested that the auditory vertex potential derived from bilateral vertically oriented dipole generators in the primary auditory cortices of the transverse temporal planes. However, W. R. Goff et al. (1969) using a linked-ear reference and Kooi et al. (1971) using a chest reference found no evidence of polarity reversal across the Sylvian fissure, and Kooi et al. moreover found that nasal electrodes picked up vertex potential activity, possibly deriving from the frontal pole. The phase reversal found with a nasal reference might therefore have been caused by the activity at the reference site. Vaughan (1974), however, has suggested that the chest reference might actually pick up activity from the base of the brain, generated by the vertical auditory cortex dipole, and might itself, therefore, be considered an active reference. In our own work (Fig. 2), we have found that, using an ankle reference, there is a definite moderate amount of activity at the nose and minimal activity at the chest reference during the period of the auditory vertex potential. In the five subjects examined, the N100 component in nose-ankle recordings was between 15 and 50% (mean 28%) of the vertex-ankle measurement, whereas there was no significant activity at this latency in chest-ankle recordings. It is difficult to presume that all the activity recorded in such a nose-ankle montage represents distant volume-conducted activity at the ankle. The relatively large amount of activity picked up at the nose might be due to the increased longitudinal as opposed to transverse current flow in the nose and nasal sinuses, allowing the recording of frontal activity at a distance. There are similar controversies about reference electrodes in visual ERP recording (e.g., Michael and Halliday 1971). For the most part, however, the chest-reference electrode as described by Stephenson and Gibbs (1951) seems to provide a relatively indifferent reference for the late components of the human evoked potential. At earlier latencies, other references might be better because of the possible muscle and spinal cord activity recorded from the chest.

Evaluation and display

Identification of components

Scalp distributions are plotted for each of the components of the recorded evoked potential. The identification of distinct EP components, however, is a very major difficulty. There are two general approaches to this problem, neither of which is completely satisfactory. The one most commonly used is to pick out a "peak" event, identify its latency, and evaluate the scalp voltage distribution at that latency. There is, however, no way of knowing that this waveform peak represents a discrete physiological event and not a recording artifact of several physiological events of similar latency and overlapping field distributions. Fig. 3 illustrates some problems of overlapping components. In the vertex and central regions of the scalp, a distinct negative-positive wave can be observed with mean peak latencies of 104 and 203 msec for eight subjects examined. At the mastoid and ear, a small negative component can be identified with a mean latency of 152 msec. In certain of the subjects, a smaller positive wave can also be distinguished at some 48 msec prior to this negative peak. In most of the subjects, these components can also be recognized in the temporal region. They probably represent a concomitant physiological event occurring in lateral and inferior temporal regions at the same time as the vertex potential. A similar temporal component of the auditory evoked response has been described by Wolpaw and Penry (1975), who by sophisticated computer subtraction procedures could identify a positive-negative complex in temporal electrodes with peak latencies of approximately 110 and 160 msec.

A second approach to the identification of EP components involves the formal mathematical analysis of the recorded waveforms. Using fairly simple mathematics, one can fit the evoked potential waveform with a series of exponentials or sine waves or other mathematical functons. Such a possible component structure is, however, quite arbitrary and not necessarily related to the underlying generators. Using more sophisticated techniques, the orthogonal "principal components" of a waveform can be obtained (John et al. 1964, Donchin 1966). These components represent those parts of the evoked potential that contribute the major portion of its variance. As such, they are determined in part by the experimental manipulations during the recording. Thus, the principal components of the visual evoked potential as derived by Donchin in 1966 delineated only those parts of the waveform that varied with the differences in light intensity used in his experiment, and had little relation to the largest EP waveform peaks, which remained fairly constant across different intensities. With sufficient experimental manipulation in both physical and psychological domains, it is probable that such principal component analysis might more fully and more meaningfully resolve the structure of the evoked potential waveform. The relationship of the principal components to physiological processes, however, is difficult to evaluate and, as has been previously pointed out (John et al. 1964, John et al. 1973, K. Squires et al. 1977), a principal factor should not be construed as representing a physiological system. Indeed, the orthogonality of the components, while greatly helpful to statistical analysis, is quite different from the interdependence of physiological systems (see also Donchin and Heffley, this volume).

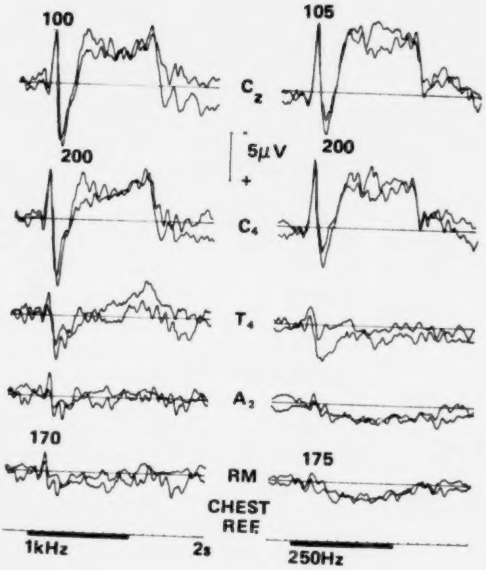

Fig. 3. Lateral scalp distribution for the auditory evoked potential obtained using equally loud (80 phon) tones of 250 and 1000 Hz. Each tracing represents the average over 100 trials.

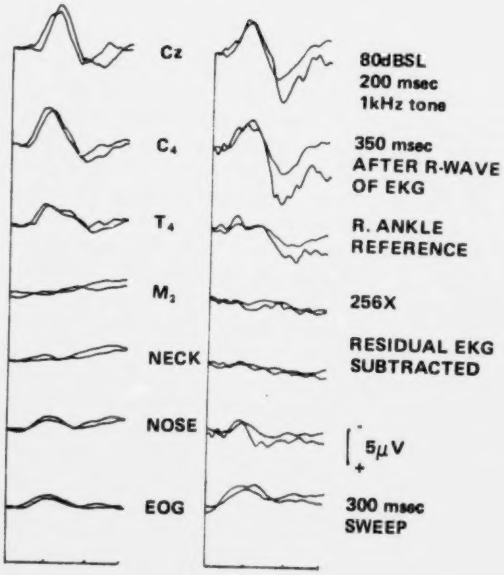

Fig. 2. Human auditory evoked potentials recorded using an ankle reference for two different subjects. The electrooculogram was recorded between supraorbital and infraorbital ridges. All other channels were recorded using a reference electrode on the right ankle.

Data display

Once the EP components have been identified, their scalp distribution can be evaluated. The technique most often used, at present, involves the selection of a latency or peak event, the calculation of individual waveform magnitudes at each electrode relative to some selected reference (e.g., the vertex electrode magnitude), the averaging of these relative magnitudes over a number of subjects, and the interpolation of contour lines. This is illustrated

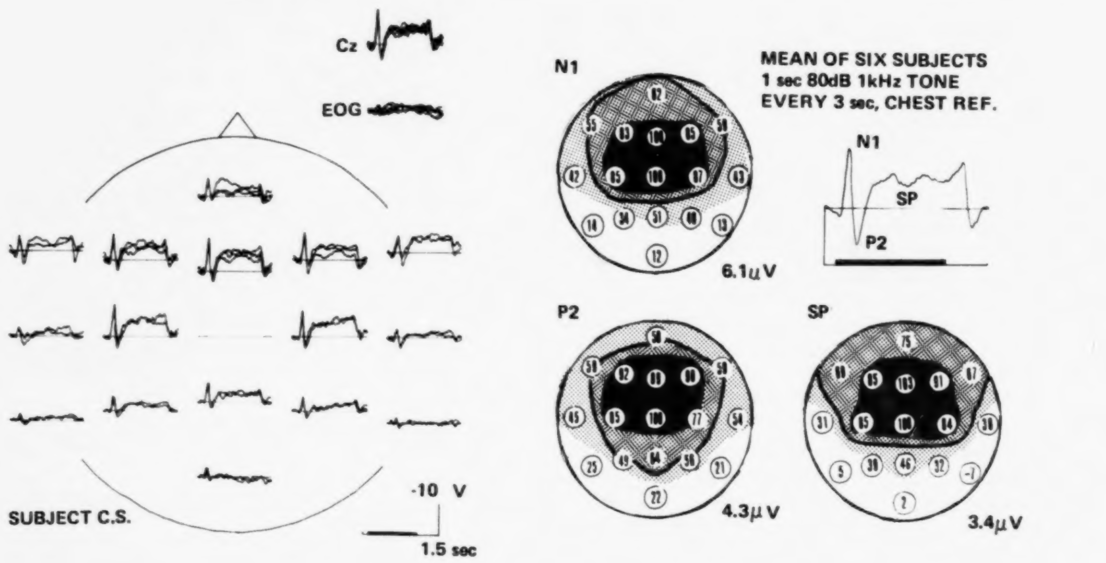

Fig. 4. Scalp distribution of human auditory evoked potential to 1-sec. toneburst. Waveforms from one subject are at the left and the mean data from six subjects are shown on the right.

in Fig. 4. The average evoked potentials for a sample subject should also be given, since this allows for the examination of the potentials at all latencies, at least in that one subject.

Time dimensions

The major disadvantage of a display system such as that described in the preceding paragraph is that the scalp topography is evaluated only at selected discrete latencies. The continuous time dimension is not portrayed, and important EP information may thus be lost (Weinberg, this volume). Without the time dimension, such things as travelling waves or spread of excitation cannot be evaluated. The temporal factor can be added to such contour maps using a moving film technique as demonstrated by Walter Freeman. If one spatial dimension is given up, a spatio-temporal map may be derived from the EP data of a one-dimensional electrode array (Rémond 1968). Interpolation of spatio-temporal contours produces a map of the evoked potential showing the sequencing of its waveforms at different locations. This type of map should be based on referential records as in Renault and Lesevre (this volume). Earlier maps based on differential recordings between adjacent electrodes and using microvolts per centimeter rather than simple microvolt contours were somewhat more difficult to understand.

Multivariate statistical analysis

The scalp distribution of an EP component is a set of measurements of that component recorded simultaneously at a number of scalp locations. The techniques of multivariate analysis are necessary for the proper statistical evaluation of such information. Multivariate statistical techniques, in particular that of principal component analysis, have been applied to evoked potentials in a number of ways (Donchin 1966). Evoked potential data in the time dimension have been analyzed to determine which temporal components of the waveform are changed by experimental manipulation (e.g., Donchin 1966, Suter 1970, Chapman 1973). Evoked potential data across both temporal and spatial dimensions have been analyzed into principal components in order to distinguish different brain states (John et al. 1973, Thatcher and John 1975), to define independent psychophysiological processes (Squires, N. et al. 1975, Donchin et al. 1975), and to evaluate evoked potential asymmetries in newborn infants (Molfese et al. 1976). The application of multivariate analysis to scalp distribution data will be considered briefly using two examples.

Differences in scalp distribution

Evoked potential components with significantly different scalp distributions must derive from different sources. Either different cells are involved in the generation of the scalp-recorded potential or the active cells are differentially responsive. The statistical evaluation of scalp distribution differences is therefore an important procedure in the differentiation of possible source mechanisms for the evoked potential. To illustrate this, we shall consider whether the scalp distributions of the onset response and sustained potential evoked by auditory stimuli (Fig. 4) are significantly different, and if so, along what dimension or dimensions this difference lies. The procedure used is based on the principal component analysis technique as described by Donchin (1966) except that electrode location is used instead of the time dimension, and replications are over different subjects rather than for the same subject. The scalp distribution of the N1, P2, and SP components for each subject was expressed as a percentage of the vertex magnitude. This procedure decreased the interindividual variability. It was also necessary since only six channels of dc data could be recorded at any one time. The principal component analysis was performed on the 17 measurements in order to obtain the scalp locations contributing most to the variance among the three evoked potential components. The first four principal components, explaining 75% of the total variance, were selected as being possibly meaningful (having eigenvalues > 1, and each contributing $> 10\%$ of the total variance). An analysis of variance was then performed for the combined scalp distribution measurements weighted by the four orthogonal dimensions defined by these principal components. Only the first factor showed any significant differentiation of EP components ($p < .01$). According to the Tukey *a posteriori* testing procedure, N1 (0.23 on the factor-weighted measurements) and P2 (0.02) were both significantly different ($p < .05$) from the SP component (-0.66) but not significantly different from each other. The first principal component was positively weighted for T6 (0.80), T3 (0.77), T4 (0.72), Oz (0.69), T5 (0.50), F3 (0.41), P4 (0.34), F7 (0.23), and Pz (0.12) and negatively weighted for Fz [(1/N)-0.30], F8 [(1/N)-0.23], and F4 [(1/N)-0.18], with the other electrodes having minimal effect (< 0.1). Thus the analysis suggests that the sustained potential is somewhat more frontal and much less posterior and temporal than the onset vertex potential.

This conclusion is supported by independent data from another experiment wherein N1 and SP were measured only at the Fz and Pz electrode locations. For the twelve subjects tested, the Fz/(Fz + Pz) ratio was significantly ($p < .01$) less for the N1 component (0.60 SD 0.05) than for the SP component (0.68 SD 0.08). Thus the auditory sustained potential has a different scalp distribution from the onset response, and must, therefore, derive from a somewhat different generator.

Identification of distinct psychophysiological events

Scalp distribution data may also be used as an added dimension to distinguish one brain event from another. To illustrate this use of scalp distribution information, the evoked potential to auditory feedback stimuli in a conceptual learning task will be examined (Stuss 1976). Eleven subjects were asked to determine repeatedly along which of five informational dimensions (e.g., color or shape) they should sort a block of 9 to 12 complex visual stimuli. The subjects made a hypothesis as to the possible sorting criterion, responded on that trial according to this hypothetical criterion, and were then given auditory feedback as to whether the response was correct (1-kHz toneburst) or incorrect (4-kHz toneburst). With repeated trials, the subjects soon learned the correct criterion and then responded appropriately until an incorrect feedback stimulus signaled a new block of trials with a different criterion. Prior to averaging, the evoked potential measurements were grouped across multiple blocks of trials according to five possible psychological conditions: "preinsight," "insight," "confirm," "overlearn," and "false feedback" (the criterion change). The evoked potential to the feedback stimuli prior to or at the time of criterion discovery (the "false feedback," "preinsight," and "insight" conditions) contained a definite late positive wave occurring with a mean peak latency of approximately 650 msec that was termed the "P4" in order to distinguish it from an earlier "P3" wave (350 msec). This P4 component is not definitely recognizable in the response to feedback in simple discrimination tasks not requiring learning (e.g., Squires, K. et al. 1973), and in our paradigm it was essentially nonexistent in trials after insight had been obtained ("confirm" and "overlearn" conditions). Since the amplitude of the P3 wave changed similarly during the different conditions, it was possible that the P4 represented merely a continuation of the psychophysiological process underlying the P3 component. The scalp distribution of the two components were, however, distinctly different, the P4 being of greater amplitude in the parieto-occipital regions (Fig. 5). These impressions of the raw data were supported when the five basic evoked potential measurements (prefeedback CNV, N1, P3, N3, P4) were submitted to an analysis of the principal components of the variance over the five conditions of the experiment and the six electrode locations (cf. Squires, N. et al. 1975; Donchin et al. 1975). It would, of course, have been preferable to submit the evoked potential data for such an analysis in a more arbitrary and extensive fashion, i.e., at multiple set latencies as in the Donchin (1966) article. Such a procedure was, however, beyond the current capacity of our laboratory. A repeated-measures two-way analysis of variance was then performed in order to assess

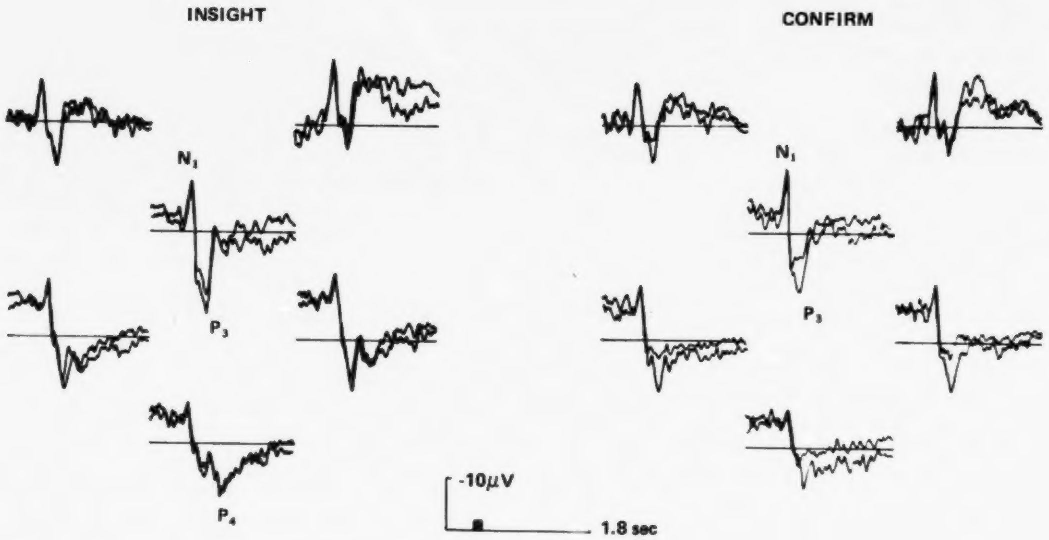

Fig. 5. Evoked potentials to feedback stimuli in one subject for two conditions of the conceptual learning task. Each tracing is the average over 12 trials.

the significance and the pattern of differentiation between the first three components (Table 1). The "P4" and "P3" components were similarly affected by experimental condition, both differing markedly from "CNV." Each of the three components had distinct scalp distributions. The "P4" component was fairly widespread in parietal, occipital, and central areas. The "CNV" was parieto-occipital, and the "P3" showed a marked vertex predominance. There are several reports in the literature describing positive waves that occur after the P3 component of the evoked potential, and their possible relationship to the P4 component that we observed is unknown. Jenness (1972) described a P4 component associated with the learning of a more accurate auditory discrimination, but this was somewhat earlier in latency (400 to 500 msec) and occurred in relation to the task stimulus rather than to the feedback stimulus. K. Squires et al. (1977) reported a positive "slow wave" component to the evoked potential to a detected signal, probably analogous to the transient return to baseline of a preceding negativity as postulated by Naatanen (1975) and Wilkinson and Ashby (1974). This slow wave, however, had a more generalized scalp distribution and a longer duration (cf. Hillyard et al. 1976) than the P4 recognized in our paradigm.

Interpretation of scalp distribution data

Inferences as to possible sources

Scalp distribution studies, in effect, involve the recording of an electrical field at a distance from one or several generators located within a volume conductor. The generation of the electrical field depends upon the separation of charge within this conducting medium. In the nervous system, such charge separation derives largely from polarization and depolarization of neuronal and glial membranes. The nature of the electrical field depends upon the extent and relationship of the activated membranes, and upon the impedance and geometry of the volume conductor. Lorente de No (1947), in his brilliant treatment of neurophysiology, identified "open," "closed," and "mixed" electrical fields (Llinas and Nicholson 1974). Recently, Rall (1970) has extended the original concept of open and closed fields and has described what might be called a "semi-closed" field. This is generated by a nuclear mass with a low resistance pathway entering at one point ("punctured symmetry"). Such a neuronal aggregate will generate a field at a distance characterized by a widespread single polarity as opposed to the dipolar nature of the open field. Finally, there is what might be

Table 1. Principal Component Analysis of Feedback Response in Conceptual Learning Task

Principal component		I"P4"	II"CNV"	III"P3"
Percentage of total variance		54.7	24.7	11.4
Weighting of raw variable	CNV	0.06	0.95	0.14
	N1	0.12	0.29	0.08
	P3	0.32	0.16	0.91
	N3	0.56	-0.05	0.32
	P4	0.90	0.10	0.31
Effects of condition	HSD[a]	1.02	0.48	0.85
	Preinsight	1.33	-0.74	1.97
	Insight	0.84	-0.95	1.68
	Confirm	0.04	-1.13	0.73
	Overlearn	0.29	-0.99	0.91
	False FB	2.37	-0.18	2.97
Effects of scalp location	HSD[a]	0.82	0.75	0.81
	Cz	1.56	-0.73	2.66
	Oz	1.01	-1.32	1.14
	F3	0.60	-0.18	1.55
	F4	0.17	-0.21	1.09
	P3	1.07	-1.36	1.54
	P4	1.41	-0.99	1.94

[a] HSD: the "honestly significant difference" between the means at $p<.05$ as determined by Tukey procedure after an initial analysis of variance.

Measurements used for evaluating the effects of condition and scalp location were obtained by multiplying raw variable measurement (in µV re baseline) by "weighting" factor as determined by principal component analysis.

termed a "diffuse field" generated through the overall separation of charge between intracellular and extracellular spaces. In an area of neurons that is diffusely excited, there is a net intraneuronal accumulation of positive charge with a resultant extracellular negativity. Depolarization of glial membranes through the release of potassium will also contribute to the extracellular negativity. Such an electrical field is similar to that of a simple current source or sink and can be recorded at a distance, albeit rapidly falling off (Somjen 1973).

An electrical field recorded at the scalp in relation to some physical or psychological event may derive from numerous, spatially separate, generators, each of which may create its own type of electrical field. It is, therefore, probably impossible to derive the nature of the source even with extensive knowledge of the resultant field. Other sources of information are often necessary for the understanding of the evoked potential and its scalp distribution: extensive animal correlative recordings (e.g., Arezzo et al. 1975), human intracranial recordings (e.g., Allison et al., in press) and human clinicopathological correlation (e.g., Michel and Peronnet 1974). At times, even such sources are insufficient for the understanding of a recorded potential waveform; e.g. human intracranial recordings define no distinct generator for the auditory-vertex potential although the multiple latency shifts suggest the presence of several sources (W. Goff et al., in press).

The interpretation of the possible origin of the auditory vertex potential is indeed a prime example of the difficulties in the inference of source from scalp distribution data (Picton et al. 1974b; Hillyard and Picton, in press). It has been variously postulated that this potential derives from a single thalamic generator (Smith et al. 1973), from deep-seated dipoles in the primary auditory cortices (Vaughan and Ritter 1970), or from widespread cortical activation in frontal and central areas (Kooi et al. 1971). Computational procedures to derive the equivalent dipole for the vertex potential (e.g., Smith et al. 1973) are of little assistance since the interpretation of this equivalent dipole remains quite difficult. As Henderson et al. (1975) point out, it is impossible to distinguish using surface recordings a real dipole lying below a convex surface (such as the thalamic or primary cortical dipoles) from synchronous activity in the surface itself (such as widespread cortical activation). In visual and somatosensory systems, "parallel late waves" occur in both the primary sensory areas and the frontocentral region (Donald, in press), and this possibility also occurs in the auditory system (cf. Wolpaw and Penry 1975, Arezzo et al. 1975). In all probability, the primary cortex, secondary areas in the temporal lobe, and widespread areas of frontal and parietal association cortex are all active during the time human auditory vertex potential appears on the scalp, and all may contribute to some extent to the scalp-recorded activity.

The interpretation of the possible source of the auditory sustained potential is equally difficult. As we have shown, its scalp distribution differs from that of the vertex potential elicited by the onset of the stimulus. The etiology of such differentiation, however, is somewhat obscure. One might postulate that the sustained potential is generated, like the onset response, in both primary and association areas, but with different contributions of each source. Mapping down the side of the scalp (Fig. 3) showed no sustained activity below the temporal region in five out of eight subjects. In three subjects, and in them only at the lower frequency, a sustained positivity was noted in the inferior electrodes. This might be due to a sustained dipole source in the primary cortex, the difference between frequencies being due to a different orientation of the primary cortex in the more lateral region of the temporal plane concerned with the lower frequencies. One might also postulate, however, that the sustained potential, like the CNV, is generated mainly in the frontal association cortex (e.g., Jarvilehto and Fruhstorfer 1973) and that the positivity represents the recording from below an activated convex plane, the differences in frequency being because of the relatively larger potential elicited by lower frequency stimuli (Picton and Woods 1975). Most probably, the auditory sustained potential, like the onset response, is generated in both the primary auditory cortex and association areas, the relative contributions of each source differing somewhat for each component.

Distinction of psychophysiological events

Although the derivation of the intracranial sources from scalp distribution data can be extremely difficult, it is somewhat simpler just to differentiate components of the evoked potential on the basis of their scalp distribution. Scalp-recorded events with different voltage distributions must derive from different sources, and therefore the evaluation of scalp distribution becomes a very powerful tool in the dissection out of distinct psychophysiological events.

Probably the most important use of such scalp distribution studies has been in the evaluation of the late positive component of the evoked potential (Hillyard et al. 1976). As was shown by Vaughan (1969), Vaughan and Ritter (1970), Picton and Hillyard (1974), Ritter et al. (in press), and Hillyard et al. (1976), the late positive wave has a different scalp distribution from the earlier components of the sensory evoked potential. Its scalp topography is also distinct from that of the preceding CNV (Donchin et al. 1975). Scalp distribution studies have further shown that the late positive potential does not represent a unitary process. Courchesne et al. (1975) have demonstrated that novel, unpredictable visual stimuli elicit more frontal late positive components than those elicited by expected signal stimuli. In the conceptual learning task reported in this paper, a distinction between the "P3" and "P4" wave of the feedback EP was made on the basis of latency and scalp distribution. This distinction makes it possible to hypothesize that the two waves reflect separate psychophysiological processes, possibly the appreciation of feedback information (P3) and its utilization in conceptual learning (P4). Such a hypothesis is tentative and will require further experimental testing to differentiate the psychological determinants of these physiologically distinct late positive waves.

Conclusion

The study of the scalp distribution of human event-related potentials is a difficult yet extremely helpful approach to our understanding of these waveforms. It provides evidence that can be used together with other experimental data to delineate the possible intracranial sources of scalp recorded events. Perhaps most importantly at the present time, it aids in the differentiation of distinct psychophysiological events occurring within the brain.

Acknowledgments

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INTRACRANIAL SOURCES OF EVENT-RELATED POTENTIALS

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Important objectives of current research in human event-related potentials (ERPs) are to ascertain the intracranial location and functional significance of the various components that can be observed in scalp recordings. Achievement of these objectives is important in providing data pertinent to psychological theories of cognitive processes (Hillyard and Picton, in press; N. Squires et al. 1977) and in clinical assessment. In addition, this information will hopefully provide the basis for future research on the mechanisms through which these functions are accomplished. At present, we have only the faintest idea what these mechanisms might be, and the task of discovering them seems awesome, especially where complex psychological processes are involved.

Many ERP investigators maintain that neurophysiologists will eventually conduct unit studies that explain the mechanisms underlying the functions ERPs reflect. This belief is comforting because it relieves the investigator of any responsibility for thinking about mechanisms, but even a cursory consideration of complex psychological processes–in particular, how brain processes produce conscious experience–exposes the naivete of that belief. Although neurophysiological achievements rank among the most satisfying and elegant accomplishments of the biological sciences, they do not even begin to suggest how biophysical events constitute conscious events. In one of the few attempts to deal with this question, John (1976) suggests both the complexity of what must be explained and the concepts of brain mechanisms that incorporate but go beyond neural activity. The end of the search, however, remains a mystery. Given the complexities and difficulties brain scientists will encounter as more information is accumulated, the attempt to locate sources of ERPs is a small step. The modesty of the goal, however, is not correlated with its difficulty.

The actual sources of ERPs consist of complex configurations of biophysical activity that produce a net separation of charge across a particular area of brain tissue. At present, investigations are essentially limited to circumscribing brain sites within which the separation of charge occurs. There are two ways in which this has been attempted. The first is to use ERP scalp distributions to test specific hypotheses based on known anatomical and other facts (Vaughan 1974). Though quite useful at times, the limitations of this approach are considerable, as detailed by Picton et al. (this volume). The other method for localizing sources of ERPs is to record directly from the brain either in man (e.g., W. Goff et al., in press) or animals (e.g., Arezzo et al. 1975). The use of animals permits extensive explorations (including successive approximations to whatever extent is required) that are precluded in human subjects, whereas the use of human subjects is essential for establishing that the ERPs being studied are identical to those recorded from the scalp and for examining ERPs unique to man.

A particularly helpful clue in localizing sources is contained in the method of transcortical recording. Dipoles that occur in the cortex produce waveforms that invert in polarity when recorded separately above and below the cortex with reference to some distant point. Although the relationship between geometrical configuration of the actual source and inversion is not known, the fact of the inversion is important. In all likelihood, most cortical ERPs recorded at the scalp derive from such dipoles.

Kelly et al. (1965) demonstrated the use of transcortical recordings in localizing sources. Median nerve stimulation was studied in monkeys by placing electrodes at many sites, above and below the cortex, and recording in monopolar fashion using a single (bone) reference. Upon stimulation, ERPs were obtained at all recording sites. The only recordings that showed inversions above versus below the cortex, however, were in the somatosensory hand area. Outside this area, ERP components were of the same polarity above and below the cortex. The interpretation of the similarity in polarity is that both recordings reflect volume conduction from a distant source. Since a given pair of electrodes above and below the cortex are in about the same geometrical position with respect to a distant dipole, components recorded from them are of similar polarity. To test this, some cortical areas where no inversion occurred were excised and filled with cotton soaked in saline. Subsequent stimulation produced the same ERPs recorded above and below the cotton, as were obtained prior to the excision, making clear the volume conducted nature of these potentials. When cortical excisions were filled with saline-soaked cotton in those areas where inversions did occur, subsequent stimulation failed to elicit inverted potentials. Inversions of ERP components above and below given portions of cortex, therefore, may be taken as an indication that those portions of cortex are sources for those components.

The transcortical recording technique has been used in monkeys to study sources of auditory (Arezzo et al. 1975) and motor (Arezzo and Vaughan 1975) ERPs. In studying auditory ERPs, they found that potentials could be elicited from all monopolar epidural electrodes (up to 60) spread out across the cortical surface. However, inversions between recordings above and below the cortex were confined to three areas: superior temporal plane, motor cortex, and lateral surface of the superior temporal cortex. There were two especially interesting features of this study. First, the volume conduction of several components that emanated from the superior temporal plane (each with somewhat different locations and orientations) could be traced from their source to surface cortex. Second, complications of effects of three main sources on surface recordings could not be disentangled without depth recordings, demonstrating the limitations of using scalp recordings by themselves for inferring intracranial sources. In the study of motor potentials, specific source locations, anterior and posterior to the central sulcus, were identified for various components associated with wrist extensions. These workers are currently using polarity inversions to locate ERP sources within specific cortical laminae. These studies are promising, therefore, for circumscribing discrete locations for sources of cortical ERPs.

To unravel the mechanisms ERPs reflect, it will be necessary to establish the functions with which given potentials are associated. The goal is not only to identify biophysical configurations that produce ERP components, but to determine how those configurations achieve functional significance. Scalp distributions can be useful in providing information about the functions related to ERPs. If two components have different distributions, it can be inferred that they have different sources and, by implication, different functions.

A good example of this pertains to the N2 component of auditory and visual ERPs. Simson et al. (1976) had subjects detect randomly omitted stimuli in a train of tones in one condition and in a train of flashes in another condition. The N2 elicited by omitted stimuli had a central focus in the auditory condition and a preoccipital focus in the visual condition (Fig. 1). By contract, P3 elicited by omitted stimuli had a parietal focus in both conditions. The N2 component had a distribution different from P3 in each modality, suggesting that the functions of N2 and P3 are distinct. Since N2 preceded P3 in both modalities, it seemed reasonable to infer that N2 reflects the detection of missing stimuli (or target selection) and P3 reflects some other process.

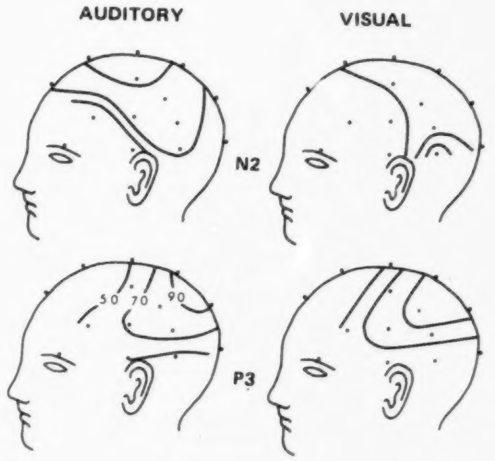

Fig. 1. Scalp distributions of N2 and P3 associated with omitted auditory and visual stimuli (grand mean of eight subjects). Dots represent electrode placements, all referred to the nose. Successive isopotential curves depict areas in which response amplitude was 90, 70, and 50% of maximum.

If the above interpretation is valid, then N2 should also be associated with target selection in vigilance tasks where targets are physically present. Simson et al. (1977) conducted a vigilance experiment where subjects were required to detect random changes in pitch embedded in a train of tones in one condition and random changes in the orientation of flashes in another condition. Since, due to overlapping latencies of the two components, N2 elicited by physically present targets is often obscured by P2, which is elicited by any physically present stimulus, ERPs associated with nontargets were subtracted from ERPs associated with targets in each condition. The resultant waveform looked similar to that elicited by omitted stimuli. The N2 component associated with targets again had a central focus in the auditory condition and a preoccipital focus in the visual condition. As with the omitted stimulus experiment, P3 had a parietal focus in both conditions (Fig. 2).

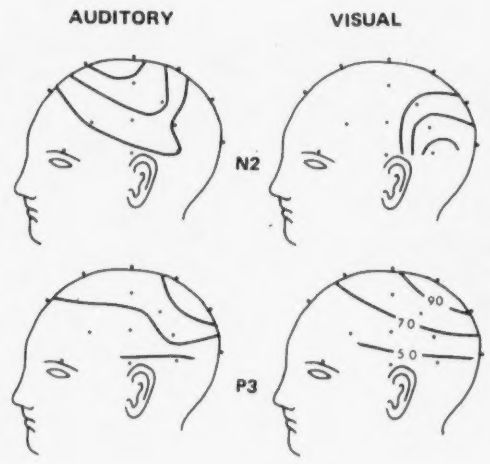

Fig. 2. Scalp distributions of N2 and P3 in auditory and visual vigilance tasks based on waveforms derived by subtracting ERPs of nontargets from ERPs of targets (grand mean of eight subjects). Electrodes and isopotential curves as in Fig. 1.

Results of these experiments, therefore, are consistent with the hypothesis that N2 is related to discrimination of targets within a given sensory modality, whereas P3 is associated with some other process that is not modality specific. The implications of these findings for the functional significance of P3 are discussed elsewhere (Ritter, this volume).

In conclusion, the purpose of investigating location of specific ERP components, along with related matters such as latency and conditions of occurrence, is to provide information useful for discovering brain mechanisms. Subsequent indentification of actual sources of specific ERP components will no doubt constitute a substantial undertaking. But that is not enough. The elaboration of brain mechanisms requires knowledge of the functional significance, as well as the neuroanatomical source, of the components under study. Determination of the functional significance of ERPs, moreover, may be a more difficult problem than localizing sources.

Consideration of function raises other important questions. Are the biophysical substrates of ERP components and their associated functions identical, or are the sources of ERPs but part of larger and more complex configurations that underlie these functions? Do the fields generated by ERP sources perhaps have functional significance, or are ERPs essentially byproducts of the brain mechanisms we seek to understand? Whether these brain events, in turn, are related to conscious experience, and if so how, is so beyond our grasp as to preclude even the most elementary speculation. The road ahead seems to get steeper the further one looks. The difficulties of the task, however, are more than matched by the importance of the goal.

SCALP TOPOGRAPHY IN THE LOCALIZATION OF INTRACRANIAL EVOKED POTENTIAL SOURCES[1]

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Topographical analysis is being used increasingly in evoked potential (EP) work. Some investigators have used it to try to separate intracranially generated from extracranially generated potentials e.g., Mast 1965, Cracco and Bickford 1968, W. Goff et al. 1969, Picton et al. 1974); others have used it to infer neural origins of presumed intracranial components (e.g., Vaughan 1969, Vaughan and Ritter 1970); still others use it primarily to infer whether or not EP components have common neural origins (e.g., Donchin et al. 1975, Simson et al. 1976) without emphasizing their location. We have recently completed an extensive topographic study including all three types of analyses mentioned above (G.D. Goff et al. 1977, Allison et al. 1977).

Somatic, auditory, and visual EPs were compared in the same subjects at all 10-20 system electrode locations plus supplementary locations to assess ocular and myogenic activity. We have also been recording intracranially from multi-contact depth electrodes and directly from the cortical surface in man. Bringing together the scalp and intracranial data permits a comparative analysis of potentials recorded from the surface and depth of the brain with their reflection on the scalp. While the topic of this symposium panel is EPs as a dependent variable without necessarily making inferences about cerebral origins *per se*, we take the position that in practice inferences about origins are implicit in any study in which topography is analyzed. Thus, our analysis provides information relevant to critical questions for this panel and for EP research in general: How useful are scalp topographies in the localization of EP generators? Under what circumstances are they accurate or inaccurate?

Since all of our cortical surface recording has been to somatosensory stimulation, we will report only somatosensory evoked potential (SEP) results. We constructed SEP scalp topographies for amplitude, using base-to-peak measurements; latency changes between most electrode locations were so small that isolatency plots were uninformative. Somatic stimulation was median nerve shock to the right wrist. Generally, we obtained six to eight replications, using averages of 64 trials per subject. The consistency of the data justified making measurements on "grand" averages for each subject.

Component identification is a problem even at one electrode location, and identification of corresponding components across locations is a still bigger problem. Component identification was aided by obtaining a grand average across subjects for each location and using this average as a guide for individual subjects. Examination of coronal and anterior-posterior arrays and construction of latency histograms were also useful in identifying components. In addition to problems of identification, arbitrary decisions have to be made about measurement methods in cases where the component appears to be distorted in various ways by other activity. Examples of methods used in this study to make base-to-peak measurements are illustrated in Fig. 1. These problems do not appreciably affect the area of maximal amplitude of a particular component, but they do affect the total region enclosed by isopotential lines. In the interpretation of any scalp topography, the particular measurement methods used in its determination must be kept in mind.

First, we will consider scalp-brain relationships for early SEP components. Fig. 2 shows schematically the first 40 msec of the SEP recorded at P3. Also shown schematically are P20 and N35 components recorded anteriorly as illustrated at Fp1. Below (in Fig. 2) are shown the topographies of these components. It is generally accepted that P15 reflects the subcortical afferent volley and that N20, P25, and

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[1] Supported by Medical Research Service, Veterans Administration, and USPHS MH-05286, RR-05358, and NSF GB-5782.

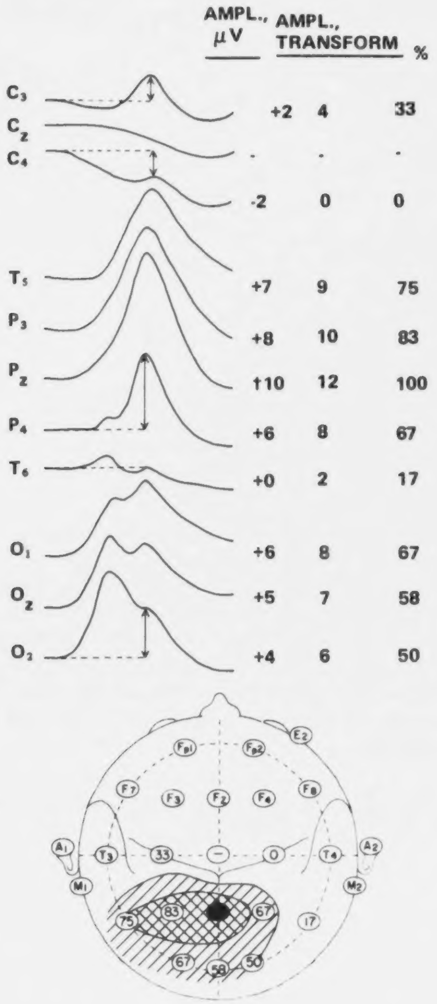

Fig. 1. Schematic illustration of measurement methods used to derive the scalp topography of an SEP "components." The topography based on these measurements is indicated below. In this and all subsequent figures, EP recording is referential to the ears, positivity is up, and stimulation is to left or right median nerve as indicated. Examples of base-to-peak amplitude measurement are shown at several locations. At Cz the component is not visible; at T6 it is visible but has a base-to-peak amplitude of zero; at C4 it has a negative amplitude; at O2 it appears only as an inflection on another component. Note that at C4, what was clearly a positive component at other locations has a negative value because the small positivity was apparently riding on a larger negativity. A similar problem is illustrated at T6 where the positivity has a zero value even though it is visually apparent.

To compensate for these cases, we transformed amplitudes by shifting the baseline for all electrode locations an equal amount so that the most negative value at any location became zero. Adding or subtracting a constant from all values does not change the relative amplitude across electrode location. After the baseline shift transformation, the largest amplitude value for the particular component was taken as 100% as shown for Pz. Other locations were then converted to appropriate percentages. The areas within which the component was 75% or greater, and between 50 and 75% of its maximum amplitude were plotted as shown in the schematic head. Isopotential lines were determined by linear interpolation between electrode locations. (From G.D. Goff et al. 1977.)

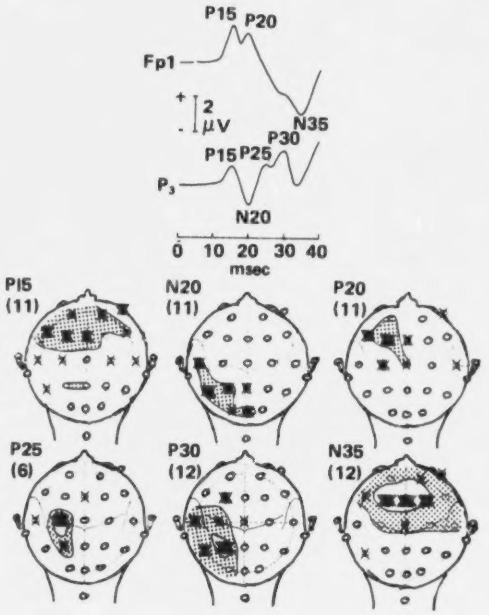

Fig. 2. Schematic of SEP early components and their topographies. X's indicate locations where in any subject the component was 90% or greater of the maximum amplitude; this indicates across-subject variability. Numbers in parentheses are the number of subjects (out of total of 12) in whom the component was observed. (Adapted from G. D. Goff et al. 1977.)

P30 reflect the primary cortical response. But after we first recorded these components (in 1960), we wondered why N20 and P30 were recorded maximally so far posterior to the presumed location of the central sulcus. In the present topographic study, we noted a positive component, P20, anterior to the central sulcus; P20 corresponded in latency to N20. We also noted a less precise but possible correspondence between the posterior P30 and the anterior N35. These topographies suggested a polarity reversal of N20 and P30 across the central sulcus, a suggestion that is consistent with the observations of Broughton (1969) recording from the cortex. The anterior-posterior relationships can be seen more clearly in selected subjects for whom the closely spaced electrode arrays shown in Fig. 3 were used. The results indicate a polarity reversal across the central sulcus, an indication that in turn suggests a dipole, oriented parallel to the surface of the cortex and normal to the bank of the central sulcus, as Broughton suggested.

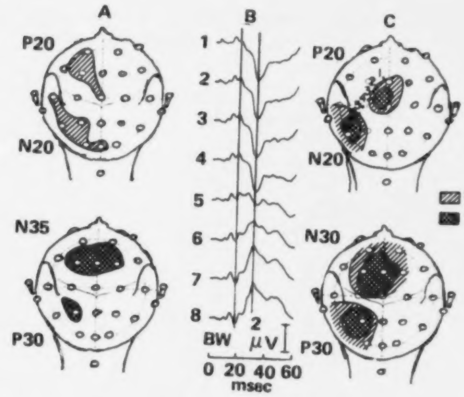

Fig. 3. SEP topography from a selected subject (Column C) compared to the group average (Column A). The potentials in Column B were recorded from the array shown on the upper head of Column C. (Adapted from Allison et al., in press.)

We compared these scalp results to direct pial surface recordings as shown in Fig. 4. Scalp records from Fz and P4 were compared to transcortical and pial surface recordings anterior and posterior to the central sulcus. Cortical surface recordings were from the right hemisphere. Both surface and scalp responses were evoked by left median nerve stimulation. Electrode 2 was a transcortical electrode with the depth probe in white matter immediately underlying the surface electrode. The polarity reversal across the central sulcus between electrodes 1 and surface 2 is clear. The *lack* of polarity reversal from surface to depth in the postcentral gyrus indicates that N20-P30 are not generated immediately under this electrode, which was located on the posterior aspect of the postcentral gyrus. Notice also that no P25 is seen. That this is due to the posterior placement of the electrode is suggested by the results from another patient (Fig. 5) in whom a more favorable electrode placement was achieved. The polarity reversal of N20-P30 between postcentral electrode 6 and precentral electrode 4 is clear. At electrode 5, which was very close to the central sulcus, a large P25 was apparent; this component does not reverse across the central sulcus but diminishes posteriorly and anteriorly. This finding suggests that P25 is generated at, or very near, this electrode and that the dipole source is oriented orthogonally to the surface of the gyrus.

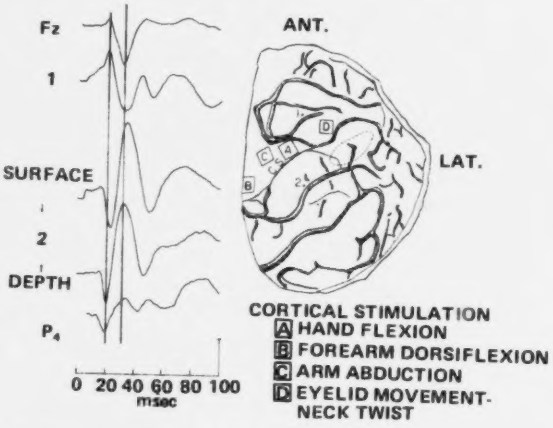

Fig. 4. Comparison of scalp and cortical records from SEP early components. Boxed letters indicate location of electrodes from which cortical stimulation elicited the motor responses listed below. C.S. indicates the location of the central sulcus of the right hemisphere. This and all subsequent cortical surface SEPS shown are grand averages of three replications of 48 individual responses. Left median nerve stimulation. (From Allison et al., in press).

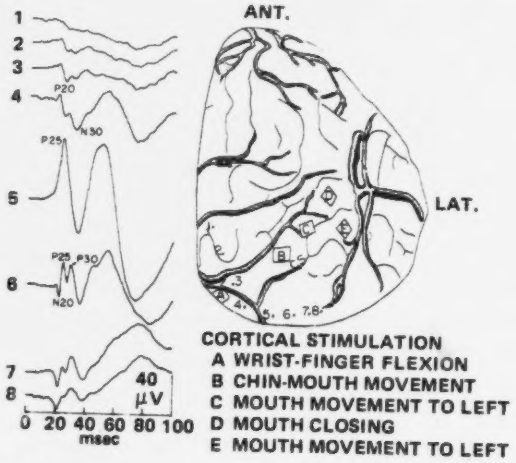

Fig. 5. Cortical surface recording of SEP early components. Other details as in Fig. 4. (From Allison et al., in press).

Fig. 6 summarizes our theories about the origins of the primary complex, N20, P20, P25, P30, and N30, and explains the observed topographies. N20 and P30 actually represent the "depth" side of the equivalent dipole source located orthogonally to the bank of the central sulcus and parallel to the surface of the postcentral gyrus as shown. Thus, at the sulcus, there is a "null" point, which explains why the components are not well recorded at central scalp electrodes, but are better recorded in the parietal area. The "surface" side of the dipole for these components is seen in scalp recordings *anterior* to the central sulcus, as P20 and N30. P20 is usually clearly seen, while N30 is seen only in selected subjects and is frequently obscured in scalp recordings by the larger N35 (Fig. 2), whose origins are unclear. P25, the equivalent dipole of which is orthogonal to the surface of postcentral gyrus, is best recorded from a restricted area of central scalp near C3 or C4 (Fig. 2).

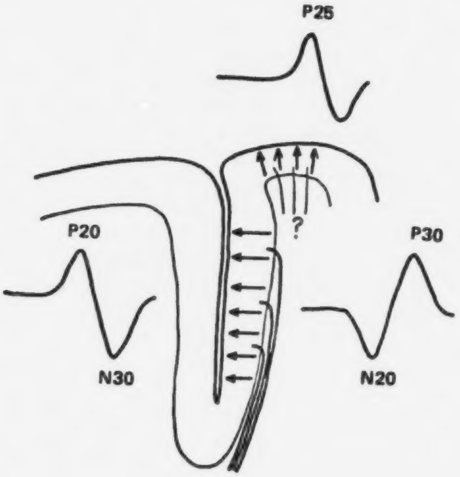

Fig. 6. Probable cortical origins of SEP early components. (Adapted from Allison et al., in press.)

Parenthetically, this interpretation of the origin of N20, P20, P30, and N30 differs from that of Papakostopoulos et al. (1975). They suggested that the precentral and postcentral components are generated independently in motor and somatic cortex because these components were differentially affected by flexion of the left index finger. Amplitude measurements from their Fig. 2 indicate, however, that N20 and P20 were unaffected by finger movement while P30 and N30 were essentially abolished. In neither case were the postcentral components (N20 and P30) differentially affected compared to their precentral counterparts (P20 and N30). Thus, the results of Papakostopoulos et al. (1975) do not contradict our interpretation that N20-P20 and P30-N30 are both generated in the posterior bank of the central sulcus.

How accurate are these scalp topographies for source location? They are reasonable for a component like P25, where there is a restricted source, the equivalent dipole of which is orthogonal to the cortical surface. They can be accurate for components like N20 and P30, where the equivalent dipole is parallel to the cortical surface if, and only if, potentials can be recorded from both sides of the dipole unobscured by other components. Then, the null point of the polarity reversal gives a reasonable indication of the source. If either side of the dipole is obscured, the topography can be misleading. We were puzzled by the parietal amplitude maximum of N20 and P30 (W. Goff et al. 1962) because we did not recognize their polarity reversal correspondence to the anterior components until Broughton's cortical recordings caused us to look for it.

An example of a scalp topography that is virtually useless in locating cerebral origins because of temporal coincidence of multiple intracranial and extracranial EPs comes from scalp-brain comparisons of SEP late components. Fig. 7 shows the topography of P100 followed by the somatic vertex potential N140-P190. The vertex potential is focused centrally around Cz and is rather diffusely distributed. P100 is shown here as having two foci. This topography is based on subjects who do *not* show a large frontal P100, such as that shown in Fig. 8. A topography based on a subject like that of Fig. 8 would not show a dual focus since the frontal P100 swamps the smaller posterior P100. Note that in this subject, P100 is still large at F7, F3, and Fz. One obtains a dual focus from subjects such as shown in Fig. 9 who have a moderate frontal P100. Note also, that in contrast to the previous figure, the frontal P100 is considerably diminished at F7 and F3 and essentially missing at Fz. At C3, its amplitude increases again and continues to increase posteriorly. We could not separate the frontal and posterior P100 on the basis of latency. The distribution of the frontal P100 suggested an extracranial response. This suggestion was supported by the fact that the frontal P100 shows great adaptation over repeated recordings; the posterior P100 does not. The frontal P100 is larger in naive subjects compared to experienced subjects and also is larger for unpredictable stimuli compared to stimuli delivered at a fixed repetition rate.

The extracranial nature of the frontal P100 and the source of the posterior P100 can be verified in direct brain recordings. We have examined records for those patients who had frontal depth probes and find no indication of an intracranially generated frontal P100. The posterior P100 appears to be intracranially generated, as shown in Fig. 10, which shows early and late SEP components recorded directly from the pial surface of the postcentral gyrus. A scalp response from Cz is shown for comparison; note the difference in amplitude calibrations. At electrodes 2 and 3, where we record the primary complex maximally (100-msec time base), we observe on the 500-msec time base a large amplitude positivity at 100 msec followed by a negative potential peaking at approximately 200 msec. Note also, that this P100-N200 complex is seen only where the primary complex is seen and only in response to contralateral stimulation. At medial and lateral locations, or in response to ipsilateral stimulation, P100-N200 is not apparent, and the waveform is more similar to that of the scalp-recorded vertex potential. We have termed this cortical P100-N200 complex the somatic late response or SLR. Fig. 11 presents similar data from another subject in whom we were able to place an array of electrodes across the central sulcus and roughly orthogonal to it. At electrodes 11, 13, 18, and 15, which progressed from the parietal area anteriorly towards the central sulcus, there are increasingly well-developed primary components on the 100-msec time base and an increasingly well-developed P100-N200 sequence on the 500-msec time base. Most important, there is a polarity reversal of the primary components between postcentral electrodes 18 and 15 and precentral electrode 7 and a similar polarity reversal of the SLR between the same electrodes. These results have been replicated in other subjects.

We can now interpret what was a very puzzling part of our topographical analysis before we were able to record directly from the cortex. There are two P100 components, as the topography based on those subjects with moderate or small P100 indicates (Fig. 7); the frontal P100 is apparently extracranially generated, probably in periocular and possibly forehead musculature, but usually does not give rise to an overt eye blink. The posterior P100 reflects an intracranial response, apparently generated in neurons either identical to, or coextensive with, those giving rise to the primary N20-P30 complex. Like N20 and P30, the polarity reversal across the central sulcus indicates that the equivalent dipole of these generators is oriented orthogonally to the bank of the central sulcus and parallel to the lateral surface of the cortex. This finding explains the posterior parietal maximum of the scalp topography of P100, similar to that of N20 and P30. On the basis of scalp topographies alone, it is not apparent that one side of a dipole is observed since the polarity reversal of P100 across the central sulcus is, it seems, obscured by the frontal, extracranial P100. Finally N200, the negativity of the SLR, is obscured in scalp recordings by the positivity of the vertex potential (P190). Thus, recognition of the existence of the P100-N200 SLR and of the location of its source would not be possible from scalp recordings alone.

In summary, a comparison of topographic data with the results of direct brain recording indicates that topographic analysis can be quite accurate in localizing the intracranial generator in the case of components generated by focal sources in which the equivalent dipole is oriented *orthogonally* to the cortical surface, as for example is the case for P25. Further, it can be accurate for a source whose equivalent dipole is oriented parallel to the surface of the cortex if, and only if, activity generated by both sides of the dipole is sufficiently uncontaminated by other potentials to be observed adequately. To know what kind of a source one is dealing with in order to interpret the scalp topographies, however, one needs to record directly from the brain. If, on the other hand, one can record directly from the brain, one does not need scalp topographies for the localization of sources. Thus, our data indicate that, in the general case, scalp topographies alone are not particularly useful in determining the locus of generation of cerebrally evoked potentials. This conclusion is consonant with a similar conclusion reached for movement potentials by Gerbrandt et al. (1973). Topographies can be useful as a dependent variable to indicate similarity or difference in the source of components without drawing any conclusions about precise cerebral origins.

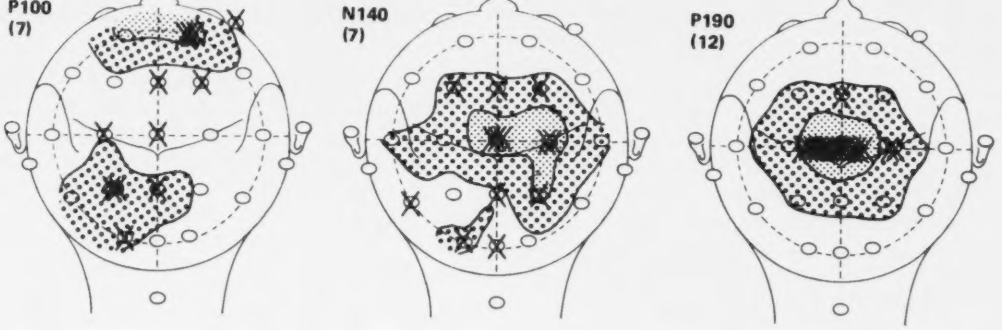

Fig. 7. Scalp topography of some SEP late components. (Adapted from G.D. Goff et al. 1977.)

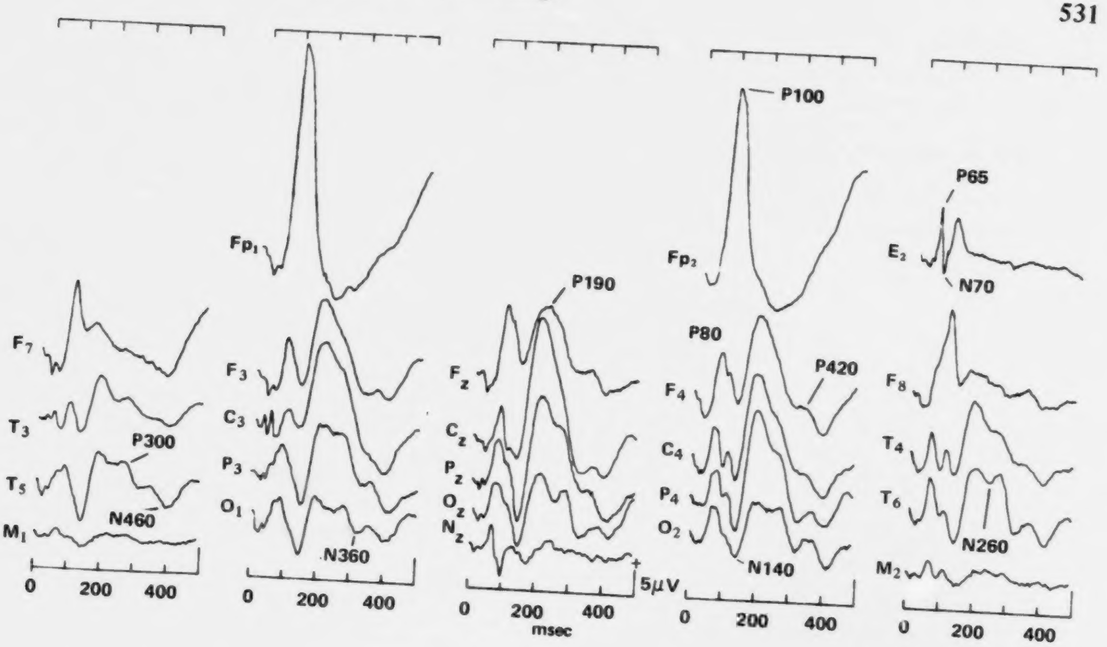

Fig. 8. Scalp SEPs recorded from a subject showing a large frontal P100 wave, largest at FP1 and FP2 and apparently generated in periocular and forehead muscles. (From G.D. Goff et al. 1977.)

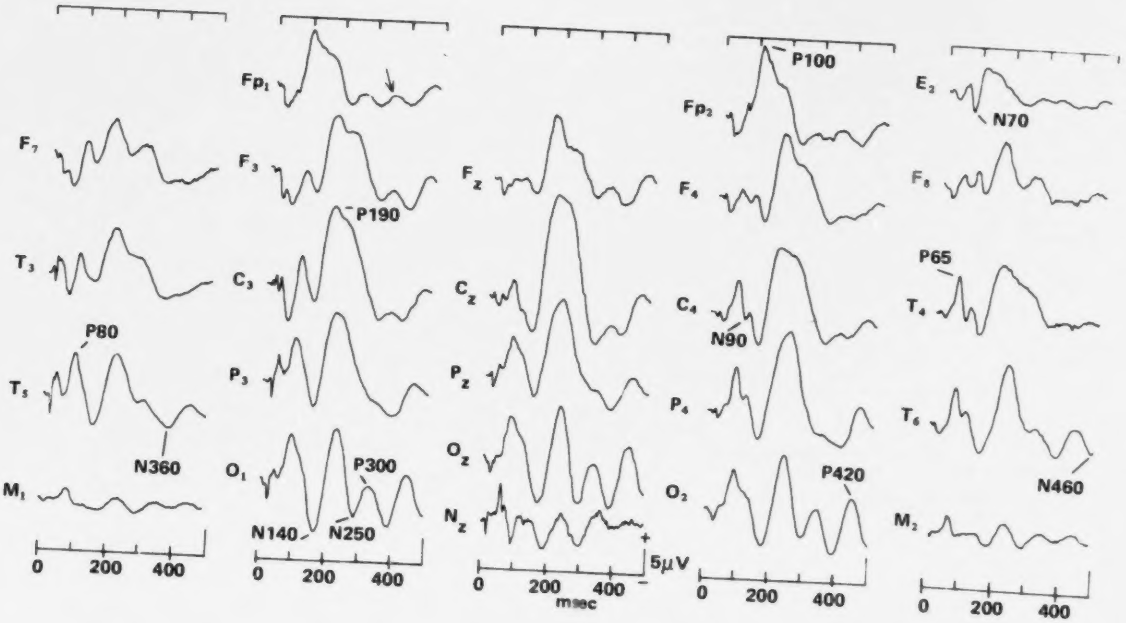

Fig. 9. Scalp SEPs recorded for a subject showing a relatively small P100 wave. (From G.D. Goff et al. 1977.)

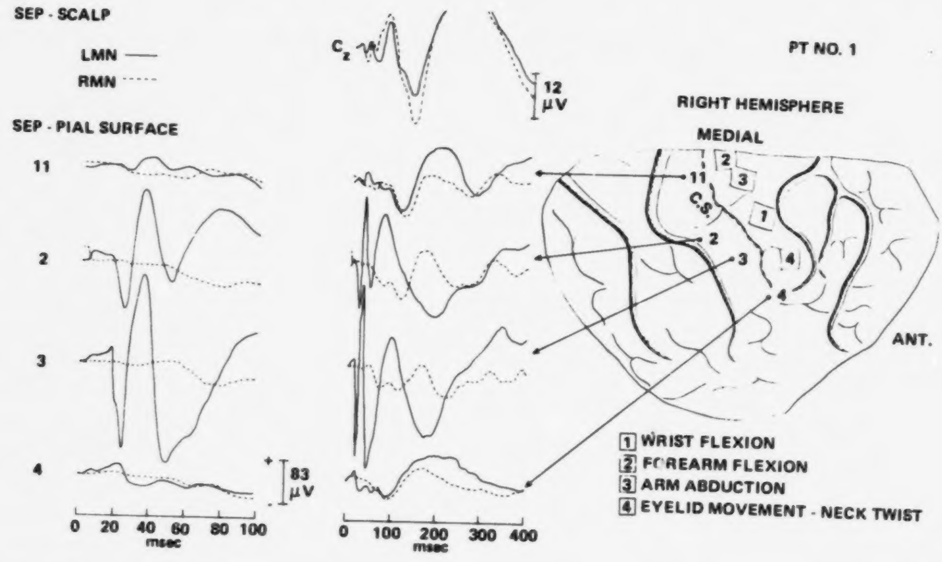

Fig. 10. SEPs recorded from postcentral gyrus. Motor responses elicited by electrical stimulation (boxed numbers) are indicated. C.S. indicates location of central sulcus. Solid traces are responses to left, and dotted traces are responses to right, median nerve stimulation. (From W.R. Goff et al., in press).

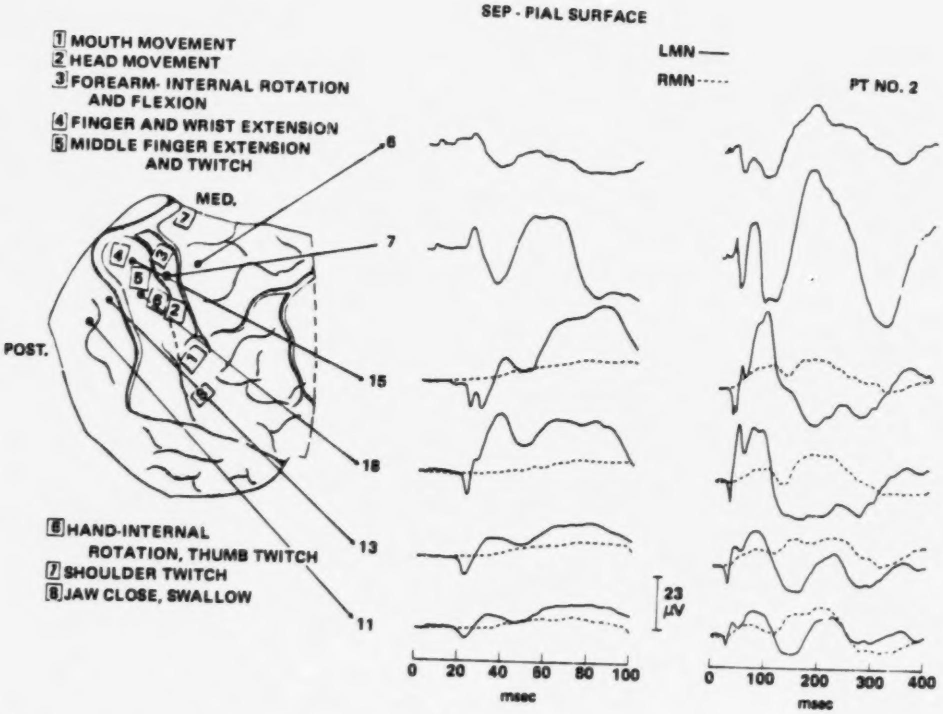

Fig. 11. SEPs recorded from pre- and postcentral gyrus. Details as in Fig. 10. (From W.R. Goff et al., in press).

SPATIAL FREQUENCY ANALYSIS OF AN EEG EVENT IN THE OLFACTORY BULB[1]

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The purpose of this paper is to describe the derivation of the spatial spectrum of the EEG recorded transdurally over the surface of the olfactory bulb in cats and rabbits. The information is needed to determine the optimal spacing of electrodes in surface arrays.

There is a close parallel here to the computation of the temporal spectrum of the EEG (Matousek 1973) recorded monopolarly with a single electrode at a point on the surface. From a single channel, a continuous record made with photographic film suffices to show the maximal and minimal rates of change of EEG potential with respect to time (temporal frequencies). When such a signal is digitized to compute its temporal spectrum, the digitizing time (the interval between measurements) is made less than half the wavelength of the maximal frequency, and the duration of the digitized record is made to exceed the half-cycle length of the minimal frequency.

It is not similarly possible to record EEG potentials in a continuous manner with respect to space. The potential must be recorded concomitantly at a set of discrete points from an array of electrodes, and the interelectrode distance constitutes the digitizing interval with respect to the spatial variable. If the maximal and minimal rates of change of EEG potential with respect to distance (spatial frequencies) are not known beforehand, the interelectrode spacing and array length must be determined empirically. From a set of digitized measurements of potential made simultaneously with a linear array of electrodes, the spatial spectrum is obtained by the same computations used for the temporal spectrum.

In this study the focus of interest was not in the EEG as a potential function but in the spatial analysis of a particular type of event or wave complex that manifested a distinctive and recurring neural activity pattern in the olfactory bulb, i.e., the sinusoidal burst that commonly accompanies each inspiration and that Adrian (1950) termed the "induced activity" as distinct from the temporally intervening "intrinsic activity."

The olfactory bulb is a part of the paleocortex, with roughly the size and shape of a pea in the rabbit and a lima bean in the cat. The outer layer facing the dura contains the afferent axons from the olfactory receptors comprising the primary olfactory nerve (PON). The innermost layer surrounding the ventricle consists of efferent and centrifugal axons, of which the most prominent set forms the lateral olfactory tract (LOT). The PON axons synapse on the apical dendrites of large excitatory neurons, called mitral cells, which send their axons in the LOT. The basal dendrites of the mitral cells form reciprocal synapses with inhibitory interneurons, called granule cells, in the middle layers of the bulb (Shepherd 1972). The negative feedback loop formed by the mitral (excitatory) and granule (inhibitory) cells is the principal mechanism for the sinusoidal oscillation of the induced wave in response to receptor input (Freeman 1975). The potential field manifested at the surface of the bulb is a dipole field generated by the granule cells that alone have the requisite location and cytoarchitecture to generate such a field (Rall and Shepherd 1968).

Spatial analysis of the bulbar-induced wave was accomplished in four stages. First, records were made from single electrodes implanted at various depths in the bulb to determine the temporal characteristics of the induced wave in both anesthetized and waking animals. Second, arrays of 60 electrodes (6x10) in a rectangular matrix were implanted on the lateral aspect of the bulb to determine the spatial distribution of the induced wave over the bulbar surface. Third, linear arrays of 64 electrodes (1x64) were implanted over identified foci of induced activity to determine the spatial frequency spectrum. Fourth, the spatial spectrum of the granule cells was predicted from volume conductor theory.

Chronic implanation was used primarily because the induced wave could be found most reliably when the animals were waking, healthy, and motiviated, e.g., by hunger, curiosity, or fear. In quiescent and anesthetized animals, the amplitude of the EEG was low, and the induced waves were usually not clearly distinguishable from intrinsic activity.

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[1] Supported by Grant MH06686 from the National Institute of Mental Health.

Methods

Observations were made on adult rabbits and cats of both sexes. Single electrodes were inserted stereotaxically through burr holes in the skull over the bulb. Electrode arrays were placed on the lateral surface of the bulb following orbital exenteration and removal of the bone overlying the bulb. In acute experiments under anesthesia (pentobarbital 40 mg/kg I.V.) the dura was also removed, but in chronic implants it was left intact.

The arrays were placed on the bulb through an opening in the skull cut with a drill just large enough to receive them. The orbit was filled with agar and closed with dental cement. Array recordings were monopolar with respect to reference electrodes over the cerebellum and in the floor of the orbit. The orbital reference was useful in abating the receptor potential from the mucosa without significantly diminishing or altering the spatial distributions of the induced waves.

The recording electrodes were stainless-steel wire insulated with Formvar. Single-channel recordings were from pairs of wires 250 micrometers (μm) in diameter, which were implanted on opposite sides of the bulbar dipole field. The 6x10 electrode arrays (4x7 mm) were of 250-μm wires at spatial intervals of 800 μm (center to center). The techniques for making the arrays for implantation have been described (Eastman 1975). The 1x64 array was made of 25-μm wire. The interelectrode distance (center to center) was 38 to 42 μm and the width of the array was 2.4 to 2.6 mm.

Signals were amplified (10k gain), filtered (3 dB falloff at 10 and 300 Hz), multiplexed, and digitized at 1-msec intervals for each channel in 100-to 900-msec epochs. Records were displayed on an oscilloscope to check for artifacts (e.g., movement potentials, open channels, polarized electrodes) and to determine the precise time locations of induced waves. Data were then written on magnetic tape for off-line processing.

Prior to each recording session, animals were deprived of food (but not water) for 24 to 48 hours. They were placed in a closed box with continuous inflow of charcoal-filtered air and given time to settle down. Odors were introduced without interrupting the air stream. Six to eight records were made of induced activity before and during the odors of food or of a chemical substance (e.g., butyric acid, amyl acetate, clove oil, methyl salicylate). Most records were taken from 1 to 4 weeks after implantation, after which the amplitudes of activity tended to deteriorate.

Postmortem dissection was done to verify the placement of electrodes and the extent of tissue reaction. Regrowth of bone under the array, dural fibrosis, and pressure marks in the bulb were observed in some animals. In those animals giving the results described here, the dura was normal in appearance and uniformally translucent over the full extent of the array, and the bulbs were slightly flattened over their lateral aspect in conformance to the planar arrays.

Off-line data processing of records from 6x10 arrays was as follows. The data comprising a single burst of induced activity lasting 80 to 300 msec were read off magnetic tape into a CDC 6400, and a graphic display of the 60 waveforms was made with the Cal Comp plotter.

For the great majority of block records showing relatively constant waveforms over the array, the spatial distributions of the amplitude and time of occurrence of the sinusoidal burst were determined. First, the mean amplitude for each channel was subtracted from the signal on that channel. The root-mean-square (rms) amplitude was found for each channel, and the 60 values were used to make a contour plot and perspective drawing by second-order extrapolation of the amplitude distribution of the induced wave.

Second, an ensemble average was made over the 60 waveforms. A product-moment correlation coefficient was computed between the ensemble average and each of the 60 waveforms. This was repeated after the waveform from each electrode was lagged +1, +2, -1, and -2 msec. The five correlation coefficients from each site were fitted with a parabola, and the most likely time lag of each waveform from the ensemble waveform was taken as the time difference between the apex of the parabola and zero time.

The dominant frequency of the sinusoidal burst was found by the Fast Fourier transform, and each time lag was expressed as a phase with respect to zero phase for the ensemble. The 60 values of phase were displayed in contour plots and perspective drawings as in the case of the amplitude distributions. In combination, these displays described the surface location, distribution, and time of occurrence (relative to the mean) of the EEG burst manifesting the induced activity.

The same computations were applied to the data from 1x64 arrays, except that the display was in the form of amplitude and phase as functions of distance along the array. The data sets were each normalized to zero mean and unit variance, and the autocovariance and spatial spectra were computed and plotted for amplitude and phase at intervals of 0.2 cycle/mm from 0 to 12.5 cycles/mm.

The correctness of the connections of the arrays of electrodes and the amplifiers was verified by immersing each array in a shallow dish of Tyrode's solution and applying an alternating current at 40 Hz across the conducting volume. The two current electrodes were placed one at each end of the array, and the reference electrode was placed several centimeters to one side of the array. When records were made and processed in the standard way, any errors in the sequence of connections were revealed by irregularities in the plots of potential versus distance. The data were rearranged by the computer.

The precision of the measuring system was determined by recording a sine wave in Tyrode's solution. In this case, one current electrode was placed close to the reference electrode and the other several centimeters distant from the array on its opposite side. With monopolar recording, the expected normalized amplitude distribution was unity and the expected phase distribution was zero. For an rms amplitude of $70\,\mu V$, simulating a typical burst of induced activity, the standard deviation of amplitude from unity was ±1.1% (±0.8μV) and the standard deviation of amplitude from unity was ±0.012 radian (0.7 degree, which is 0.002 cycle, equivalent at 40 Hz to 0.05 msec). On this basis, the system was judged to be capable of discriminating lag time differences in EEG patterns on the order of 1/20 of the digitizing time interval (1 msec). For low-amplitude or low-coherence signals, the precision fell off rapidly.

Results

Spatiotemporal patterns of induced waves in the bulbar EEG

The typical form of the olfactory bulb EEG and its relation to respiration are shown in Fig. 1. With each inspiration there was a surface-negative, deep-positive (Fig. 1a, lower trace, downward positive) shift in potential that reversed with expiration (downward in the upper trace). When it occurred, the sinusoidal burst was seen to start and end slightly after the start and end of inspiration. When the low frequency wave was filtered out and the respiratory rate was slowed (Fig. 1b), the distinction between the intrinsic (between bursts) and induced activities was most clearly seen.

Fig. 2 shows an example of the 60 waveforms recorded from the surface of the bulb and anterior olfactory nucleus of a rabbit during a single burst. Fig. 3 shows the amplitude and phase distributions derived from the olfactory bulb of a cat. The bottom of each frame represents the anterior aspect of the left bulbar surface, and the right edge corresponds to the ventral edge of the bulb.

In each of 6 cats and 12 rabbits, the following features were found. There were one to several localized domains of high amplitude activity either within the borders of the array (Fig. 3) or (by extrapolation) adjacent to the array. These foci were irregular in size, shape, and location, varying unpredictably from animal to animal. However, for each animal they were relatively constant in location and form over several weeks of observation. Variations were analogous to those of a signature that has a certain pattern, but is never twice the same. On visual inspection, the variation in pattern appeared to be no more or less between two successive bursts during presentation of a certain odor than it was for two bursts recorded at different times or on different days in response to different odors. There was no apparent relation between the size, shape, or location of foci and the type of odor presented, the overall amplitude or duration of the burst, or the kind of motivational state, except that bursts were reproducibly observable only if some form of motivation was present (as implied by food deprivation, nociceptive stimulation, exploratory behavior, aversive behavior, etc.).

The phase plots over the bulb were somewhat less regular than the amplitude plots. That is, the pattern for each animal was clearly recognizable from trial to trial, but the irregular variations were greater than those for amplitude. The maximal and minimal values for phase most often occurred near to, but not at, the amplitude peaks. A typical pattern revealed a phase maximum and phase minimum on opposite sides of an amplitude peak in a focus of activity (Fig. 3). In about half the animals, there was a persistent weak phase gradient across the array in the direction of PON axonal conduction (anterior to posterior), with phase lead (positive values) anteriorly and phase lag (negative values with respect to the mean) posteriorly. In records from the other animals, there was a weak dorsoventral phase gradient or no gradient.

Spatial spectral analysis of induced waves

The fine structure of active foci recorded at the surface was explored by placing 1x64 arrays across them. Initially, five of the animals with implanted arrays were re-anesthetized with pentobarbital. The relatively weak induced activity present under anesthesia was recorded and processed. The amplitude and phase distributions were less precise due to the lower amplitudes, but the spatial distributions were similar to those found in the waking state.

With this assurance, a 6x10 array was placed on the bulb of an anesthetized animal and the location of a focus was determined. Then the 6x10 array was replaced with a 1x64 array running from anterior to posterior across the maximum of the focus. Five animals (three rabbits and two cats) were implanted in this manner.

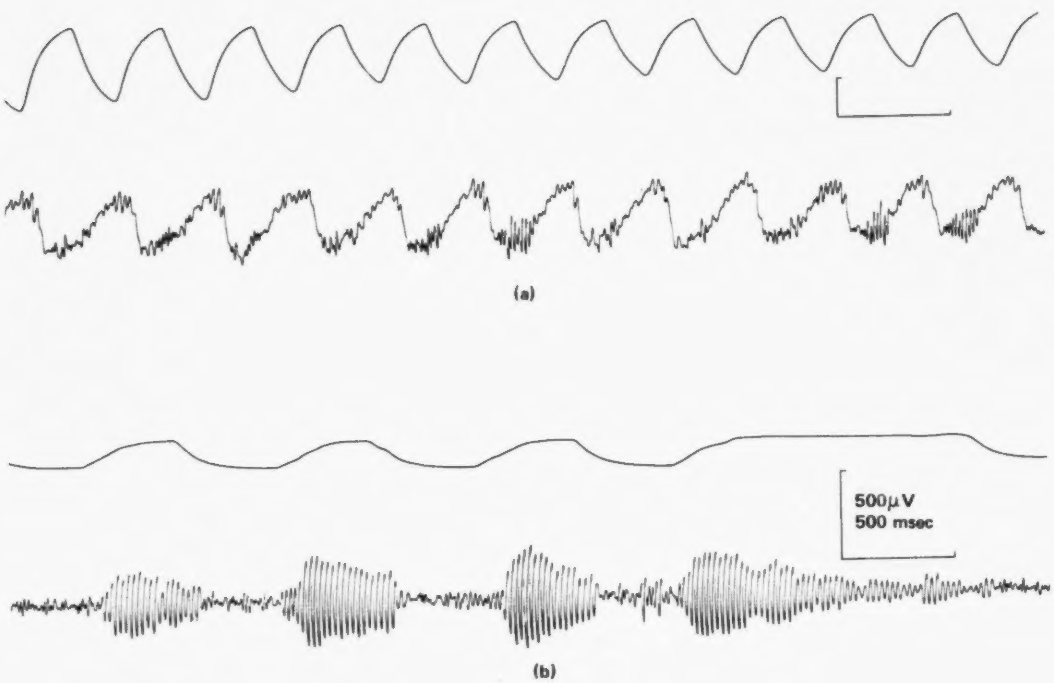


Fig. 1. (a) EEG bipolarly recorded (lower trace, negative upward) from the olfactory bulb of a waking rabbit (inner with respect to outer layers) and respiration recorded (upper trace, inspiration upward) with a thermocouple in the ipsilateral nares. EEG filter settings: 0.1 Hz/1 kHz. (b) EEG from anesthetized rabbit after tracheotomy with pump-controlled airflow through nares. Filters settings: 10 Hz/1 kHz. From Freeman 1976.

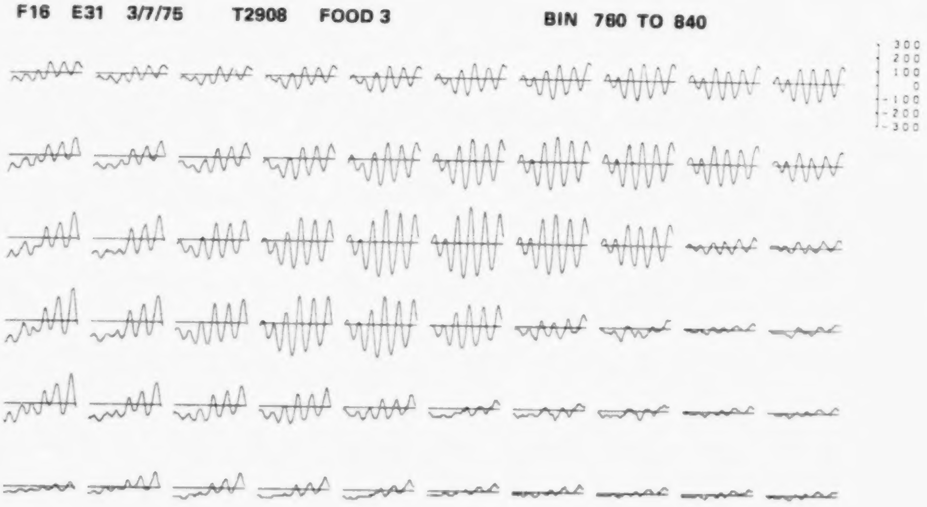
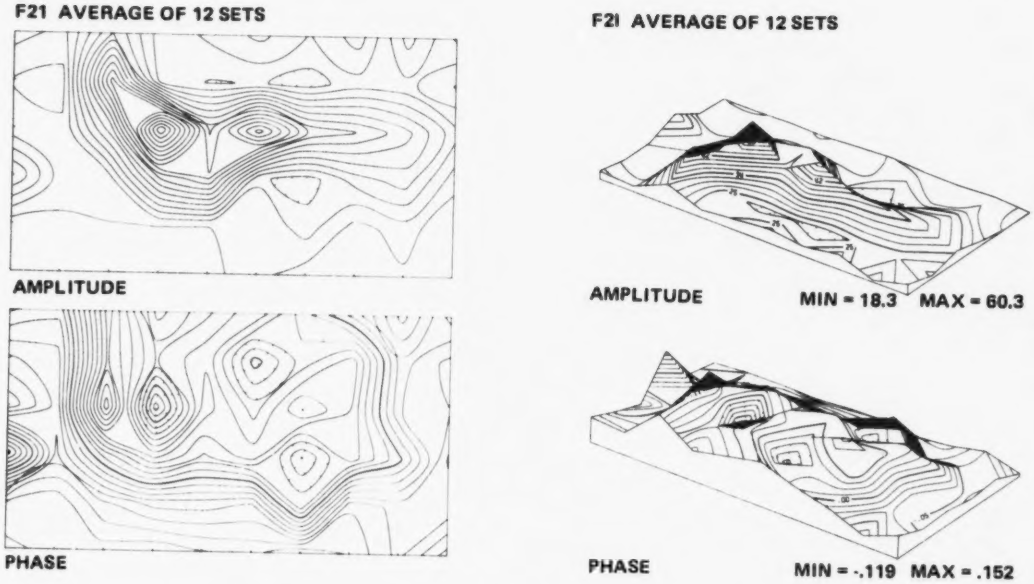


Fig. 2. Concomitant EEG records of an induced wave in a waking rabbit from a 6x10 electrode array (4x7 mm) placed over the left bulb and anterior olfactory nucleus. Left side is anterior, top is dorsal. Duration of record, 80 msec. Calibration in µV.



F21 AVERAGE OF 12 SETS

F2I AVERAGE OF 12 SETS

Fig. 3. Upper frames: Contour (left) and perspective (right) plots of amplitude distribution of induced waves over the left olfactory bulb of a cat recorded with a 6x10 array (4x7 mm). Left side is dorsal; bottom is anterior. Range of rms amplitudes, 18 to 60 μV. Lower frames: distribution of phase values. Range, -0.119 to +0.152 radian (6.8 to 8.7 degrees).

Induced activity was recorded and processed as before in the presence of filtered air, the odor of food, and a chemical odor. Amplitude and phase displays (Fig. 4) were consistent with the appearance of cross sections through contour plots as previously displayed (Fig. 3).

The Fourier transform was taken of single amplitude and phase plots and of the autocovariance function of sets of three to six plots placed in series. In the latter procedure, individual records were detrended to remove amplitude and phase gradients extending the full length of the array. The lower cutoff spatial frequency was 1/(2.5 mm), or 0.4 cycle/mm, and the upper frequency was 1/(2x40μm), or 12.5 cycles/mm. The procedure was also applied to records from anesthetized animals and from arrays in Tyrode's solution as controls.

A set of ten pairs of spectra for amplitude and phase from a cat (F42) are shown in Fig. 5. Records were taken in pairs on different days over a period of 2 weeks. Each pair was during exposure to filtered air and to an odor. Maximal amplitude and phase values were observed between 0.4 and 1.0 cycle/mm. The locations of peaks varied unpredictably from trial to trial. A comparison is made in Fig. 6 between the spectra for amplitude from ten animals under anesthesia (upper frame), five waking animals (upper five curves in the lower frame) and five control records in Tyrode's solution (lower five curves in the lower frame). Some records from anesthetized animals showed spectral peaks near 0.6/mm, but most were relatively flat, consistent with the low amplitude of the induced activity in that state. Control spectra were uneven over most of the spatial frequency range. This was the result of the normalization to unit variance, which accentuated the variations due to noise. Activity present in waking animals in the band from 0.6 to 1.0 cycle/mm was not present in control and anesthetized records.

The data are summarized in Fig. 7 as the averages of ten spectra from anesthetized animals, ten control spectra, ten spectra from F42, and ten spectra from five waking animals (two from each). The significant feature is a spectral peak in amplitude spectra from waking animals near 0.8 cycle/mm that is absent from the other spectra. There is no corresponding peak in the phase spectra.

Theoretical evaluation of the spatial spectrum

The bulbar field of potential in response to electrical stimulation of the PON or LOT was found to have the same dipole structure as the field of the EEG (Freeman 1972, 1975). When a recording microelectrode was inserted perpendicular to the bulbar

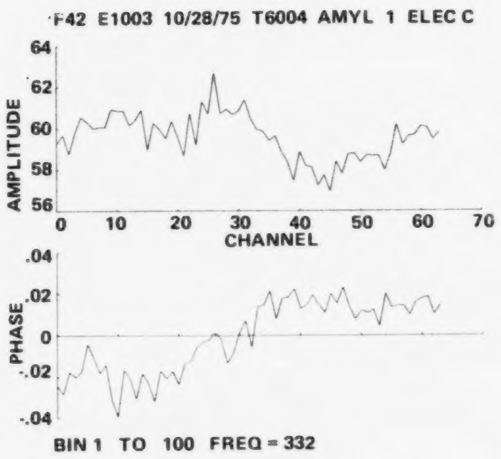


Fig. 4. Distribution of rms amplitudes (upper frame) and phase (lower frame) of an induced wave recorded from the surface of the olfactory bulb of a waking cat (F42) with a horizontal 1x64 array 2.6 mm in width. Right is anterior.

surface through the epicenter of an evoked response, the potential with respect to a distant point at the crest of the initial surface-negative peak of the granule cell response (and the peak-to-peak amplitude of the subsequent damped sine wave oscillation) went to a maximum at a depth of 600 to 700 μm, to zero at 800 to 1000 μm, to a minimum at 1100 to 1300 μm, and toward zero at greater depths (data points in Fig. 8). The depth profile was fitted with a curve of potential (solid curve, Fig. 8), which was generated by a core conductor simulating the current source-sink distribution of the granule cell population (dashed curve, Fig. 8).

As previously described (Freeman 1972), the granule cell was treated as a cylindrical core conductor oriented perpendicular to the bulbur surface with its midpoint lying at a depth of 1000 μm. The synaptic input was to the upper half of the cylinder, and the lower half was passive. During an EPSP, there was inflow into the upper half and outflow from the lower half. The sink-source relation was reversed during an IPSP. In either case, the source sink density was approximated by a double exponential curve of fixed charge density, q

$$\begin{aligned} q_n &= e^{-z_n/\lambda}, \qquad & z_n &< 0 \\ q_n &= -e^{z_n/\lambda}, \qquad & z_n &> 0 \end{aligned} \tag{1}$$

where z was the axis of the cylinder oriented perpendicular to the bulbar surface and $\lambda = 170\,\mu$m was the experimentally determined length constant of the granule cell (dashed curve in Fig. 8).

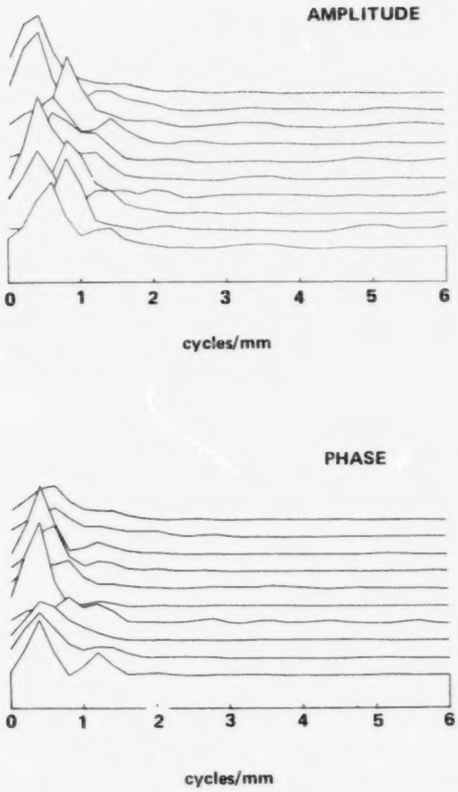


Fig. 5. Ten spectra of amplitude and phase from a waking cat (F42), taken in pairs on separate days. The rms amplitude and phase values were normalized to zero mean and unit variance prior to spectral analysis. The variation in spectra was not related to odor.

The surface coordinates of the bulb were x and y. The potential, $v_m(x)$, at a set of points representing m recording sites at x_m on the surface along x (where $y_m = 0$) for a single granule cell at $x_o = 0$ and $y_o = 0$ was given by

$$v_m(x) = \sum^{p} q_n \Big/ \left[(x_m - x_o)^2 + (y_m - y_o)^2 + (z_n - z_o)^2\right]^{0.5} \tag{2}$$

where z_o was the depth of the midpoint of the cylinder. The potential field for a population of granule cells was given by specifying a distribution of sources and sinks over x and y with equation (1) and summing the potential with equation (2), giving the solid curve in Fig. 8.

The bulbar input from electrical stimulation of the PON or LOT activated a distribution of granule cells in the bulb, and the potential at the surface had a bell-shaped distribution. The size of the active focus was estimated from the half-amplitude width of the

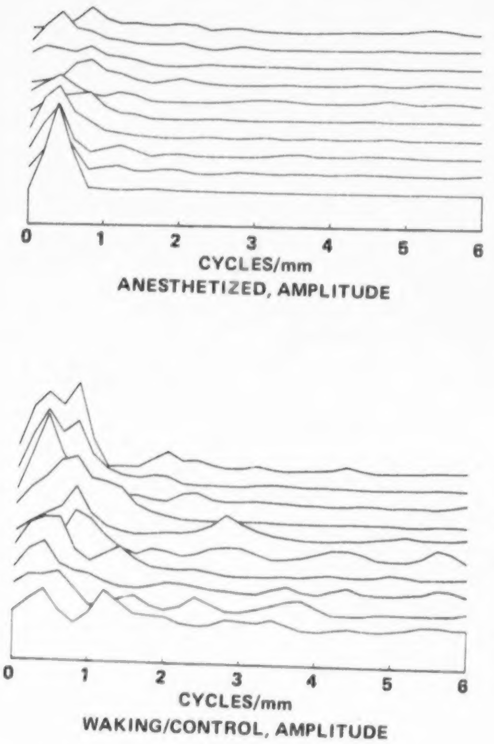


Fig. 6. Upper frame: amplitude spectra from four cats and six rabbits under pentobarbital anesthesia (40 mg/kg i.v.). Lower frame: upper five traces, amplitude spectra from two cats and three rabbits in the waking state with implanted 1x64 arrays; lower five traces, amplitude spectra from records of sine wave signals recorded in Tyrode's solution at 40 Hz and 70 μV rms.

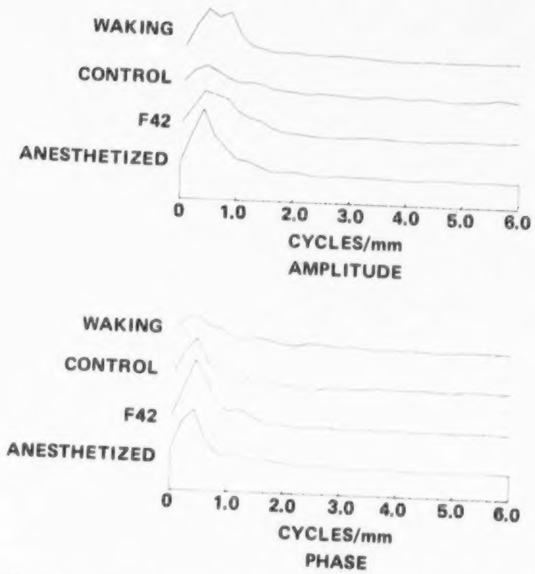


Fig. 7 Averaged spectra for amplitude and phase from ten anesthetized animals, ten records from a waking cat (F42), ten control records, and ten records from waking animals.

surface peak of potential. If the width of the active focus was reduced, the width of the surface peak of potential was also reduced (Fig. 9). Over most of the range, the relation between the width of the focus and the half-amplitude width of the field of potential was linear. For small widths approaching zero, the half-amplitude diameter of the potential field approached a limiting value. By extrapolation, if a single granule cell were activated, its field of potential recorded at the surface would be bell-shaped with a half-amplitude width corresponding to the limiting value. The minimal-width curve of surface potential with distance from the epicenter is shown in Fig. 10, lower frame, solid curve. The points were computed from equations (1) and (2). They were fitted by nonlinear regression with an empirical curve

$$g(x) = k_1 \left(e^{-x/\lambda_1} - k_2 e^{-x/\lambda_2} \right) \qquad (3)$$

The values of the coefficients are given in the legend for Fig. 10.

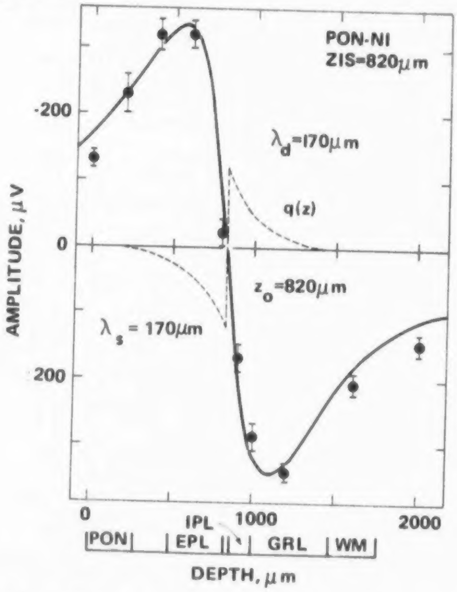


Fig. 8. Points show the means and standard errors of the peak amplitude (N1) of the averaged evoked potential with depth in micrometers from the surface on PON stimulation. Dashed curve is the postulated source-sink distribution for the granule cell as a function of depth as in equation (1). Solid curve is the potential as a function of depth calculated from equation (2). From Freeman 1972. λ, length constant of granule cell; z_o, site of membrane current reversal; ZIS, zero isopotential surface.

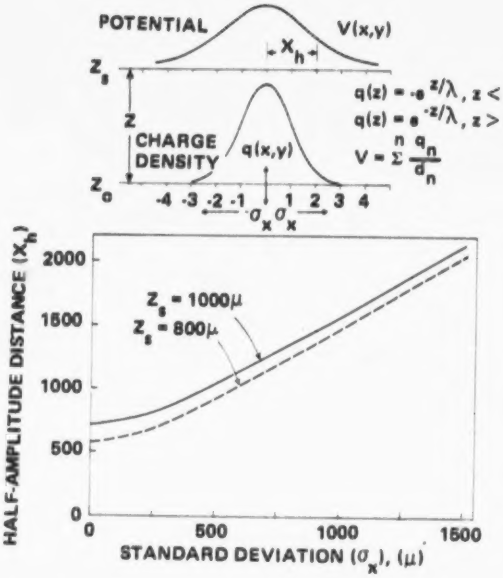


Fig. 9. Relation between the half-amplitude width of a surface distribution of potential (ordinate) and the width of an active focus of granule cells expressed by the standard deviation, λ of a normal distribution. For near-zero width, the width of the surface field of potential approaches a limiting value. From Freeman 1972.

The activity of a single granule cell was treated as a spatial delta function, and its surface field of potential as an impulse response. If a distribution of granule cells were activated by an input u(x), the potential fields of all the cells would be superimposed in the volume conductor to give the observed field of potential v(x). This operation of summation was represented by convolution

$$v(x) = \int_{-\infty}^{\infty} u(x)\ g(x-X)\, dX \tag{4}$$

Alternatively the operation was expressed by taking the two-sided Fourier transform of equation (4).

$$V(j\omega_x) = U(j\omega_x)\ G(j\omega_x) \tag{5}$$

The spatial frequency, ω_x (radians/mm), was $2\pi f_x$ where f_x was the spatial frequency in cycles/mm.

When the input was a spatial delta function, then $U(\omega_x) = 1$ and

$$V(j\omega_x) = G(j\omega_x) \tag{6}$$

Then, from the Fourier transform of equation (3)

$$G(j\omega_x) = k_1\left(\frac{2\lambda_1}{\lambda_1^2\omega^2 + 1} - k_2\frac{2\lambda_2}{\lambda_2^2\omega^2 + 1}\right) \tag{7}$$

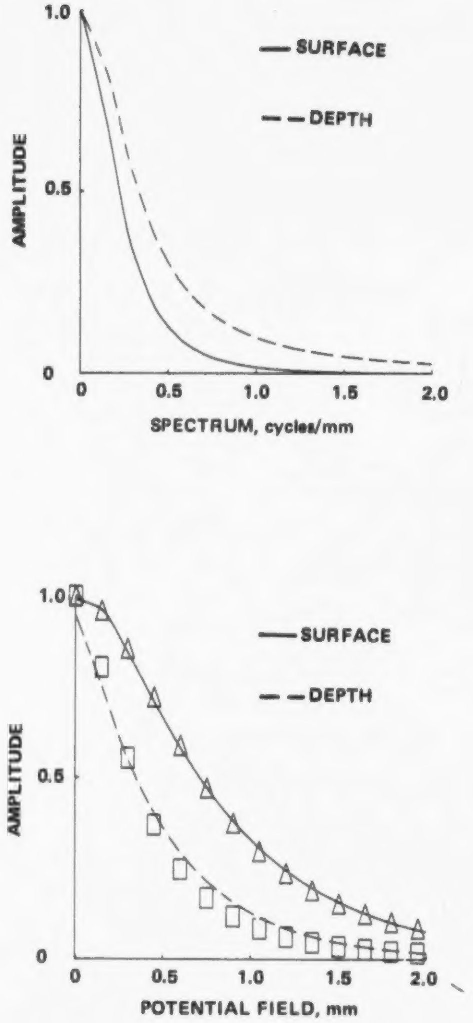


Fig. 10. Lower frame: symbols show the potential as a function of distance in mm from the epicenter of an active focus of near-zero width, calculated with equations (1) and (2). Solid curve and triangles: predicted potential for an array of electrodes at the surface (1000 micrometers from ZIS). Dashed curve and rectangles: predicted potential from an array at a depth of 500 μm from ZIS. Curves are from equation (3). Solid curve: $\lambda_1 = 670\,\mu m$, $\lambda_2 = 190\,\mu m$, $k_1 = 1.50$, $k_2 = 0.33$. Dashed curve: $\lambda_1 = 480\,\mu m$, $\lambda_2 = 9.3\,\mu m$, $k_1 = 1.03$, $k_2 = 0.08$.

Upper frames: Fourier transforms of the curves in lower frame from equation (7) and normalized to unity at $f_x = 0$. These are the transfer functions describing the attenuation by the volume conductor of the EEG amplitude from surface and depth records generated by differing spatial frequencies of granule cell activity.

Spatial Frequency Analysis

The amplitude function from equation (7) was the transfer function or weighting curve (Fig. 10, upper frame, solid curve), which showed the attenuation effected by the volume conductor on the surface field of potential as a function of the spatial frequency of granule cell activity. This curve predicted that the spectrum of the potential recorded at the surface should fall sharply between 0.5 and 1.5 cycles/mm and should be essentially zero at higher frequencies.

In comparing the spectral curve in Fig. 10 with those in Fig. 7, it should be noted that the experimental data were set to zero mean and unit variance (and in some cases were also detrended). This had the effect of passing the data through a low-cutoff spatial frequency filter with a characteristic frequency of 0.4 cycle/mm. The purpose of this procedure was to reduce the zero frequency peak of the experimental curves, which otherwise resembled the solid curve in Fig. 10 (upper frame), in order to accentuate (for display purposes) the spatial variations at rates above 0.5 cycle/mm, up to the limits of resolution at about 1% of maximal rms amplitude. Hence the decline in amplitude spectra shown in Fig. 5 to 7 between 0.6 and 1.0 cycle/mm is comparable to the decline in the solid curve in Fig. 10 (upper frame) over the same frequency range.

The question whether a better resolution of spatial frequency of the EEG might be attained by recording in a plane parallel to the surface, but at a depth near the maximum of the granule cell dipole field, was considered. The expected distribution of potential with distance from the epicenters at a simulated depth of 500 μm is shown in Fig. 10, upper frame, by the dashed curve. The Fourier transform is shown in Fig. 10, lower frame, also by the dashed curve. The cutoff spatial frequency was raised to 1.5 to 2.0 cycles/mm.

Discussion

The experimental results indicated that induced EEG waves recorded at the surface of the olfactory bulb were spatially nonuniform and appeared as localized active foci. The foci were irregular in outline, averaged 1 to 3 mm in half-amplitude width, varied in shape and location between animals, but were relatively invariant for each animal. These activities were recorded in waking animals with 6x10 arrays. The interelectrode distances were 0.8 mm and the size of the arrays was 4x7 mm. The area of the array (28 mm^2) was about 16% of the estimated total surface area (176 mm^2) of the bulb in the cat. The rabbit bulb was smaller, but only part of the array could be fit over the bulb; the rest of the array overlay the anterior olfactory nucleus, so that the array covered about 17% of the bulb of the rabbit. The area in which induced waves were observed above half-amplitude was less than one-fourth of the electrode area in all animals. By extrapolation, less than 25% of the bulb was responsible for the appearance of induced waves. In some preparations there was no induced activity within the array. The trauma of surgical implantation may have been responsible for this, and perhaps for the spotty distribution of induced activity as well.

The spatial frequency spectrum across such foci was determined with concomitant records of potential from 1x64 electrodes averaging 2.5 mm in length and 40 μm in interelectrode distance. The maximal observed spatial frequencies in records from waking animals ranged from 1.0 to 1.5 cycles/mm (Fig. 5 to 7). This upper limit was consistent with the known volume conductor properties of the neurons generating the EEG (Fig. 10). This implies that the desired interelectrode distance for spatial analysis is from 0.5 to as low as 0.33 mm, or perhaps even less, for recording surface distributions of the induced waves.

The recording system used was limited to 64 channels. An 8x8 array at 0.5-mm spacing is 3.5x3.5 mm, and the area (12 mm^2) is 7% of the cat bulb or 17% of the rabbit bulb. An 8x8 array at 0.3-mm spacing is 2.1x2.1 mm(4.4 mm^2), which covers 2.5 and 6% of the bulbs, respectively, of the cat and rabbit. These dimensions would appear to suffice for the study of a single active focus, but they pose difficulty in the localization of a focus, particularly under anesthesia when the induced waves tend to be poorly defined.

Theoretical analysis shows that little is to be gained in spatial resolution of the EEG by attempting to place the electrodes within the bulb rather than on its surface. The attendant surgical damage would be prohibitive.

The upper limit of the spatial frequency of the EEG does not address the question of whether neural activity in the bulb occurs at relatively higher spatial frequencies. Indeed the input synaptic region of the bulb in the glomerular layer has a mosaic appearance (Freeman 1975), suggesting that the PON input is spatially "coarse grained" by parcellation into synaptic subdomains, in a fashion analogous to the parcellation of input by the compound facetted eye of an insect. The average diameter of the glomeruli in the cat is 135 μm. If this is treated as a half wavelength, the implied spatial frequency of bulbar activity is 3.7 cycles/mm. If such spatial variations in activity level occur, they are inaccessible in EEG recordings due to the smoothing effect of the volume conductor in which the generating neurons lie. The presence of activity between 0.6 and 1.0 cycle/mm in the spectra from waking but not from anesthetized cats and rabbits indicates that neural activity does occur with spatial rates of change in excess of 1.0 cycle/mm, although its manifestation in the EEG is sharply curtailed.

The detailed application of these techniques to other structures and spatial activity patterns in the brain (Petsche 1972) appears to be conceptually straight forward in terms of defining particular reproducible events in the EEG, measuring their time courses and spatial distributions, and computing their temporal and spatial spectra. The rate of fall-off of spatial spectra with increasing spatial frequency depends on the geometry and particularly on the depth of the generating neurons, so that the forms of the spatial frequency spectra for other events cannot be predicted without detailed anatomical and electrophysiological specifications. However, for purposes of modelling volume conductor properties, particularly in gauging the attenuation of spatial frequencies in going from cerebral to scalp recordings, the value for spatial frequency of 1 cycle/mm may be particularly useful.

Summary

An approach for experimentally measuring and theoretically predicting the spatial frequency spectrum of a component of the EEG is described. A particular recurring waveform in the EEG of the olfactory bulb (the "induced wave" of Adrian) of cats and rabbits is described in terms of its time course, spatial distribution at the surface of the bulb, and depth distribution within the bulb. The spatial spectrum is computed from the Fourier transform of amplitude distributions determined concomitantly from 64 electrodes spaced along a line on the bulbar surface at intervals of 40 μm. The observed spectra fall off rapidly in amplitude between 0.6 and 1.0 cycle/mm. This result is consistent with the known volume conductor properties of the neurons generating the bulbar EEG. This does not exclude the occurrence of neural activity at higher spatial frequencies, but it implies that such spatial variations are not reflected in the EEG, and that electrodes need not be spaced closer together than 0.3 to 0.5 mm to extract the available information about the spatial structure of the bulbar EEG waves.

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IX. ALTERNATIVES TO SIGNAL AVERAGING

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ALTERNATIVES TO SIGNAL AVERAGING: EXCERPTS OF PRECONFERENCE CORRESPONDENCE

Prepared by H. Weinberg, Panel Chairman and Section Editor

The following correspondence was conducted prior to EPIC IV by the panel on Alternatives to Signal Averaging. Members of the panel included:

1. H. Weinberg (chairman), Brain Behaviour Laboratory, Simon Fraser University, Vancouver, British Columbia, Canada.
2. L. K. Gerbrandt, Department of Psychology, California State University, Northridge California.
3. R. Herning, Langley Porter Neuropsychiatric Institute, San Francisco, California.
4. E. R. John, Brain Research Laboratories, New York University Medical Center, New York, New York.
5. P. Naitoh, Naval Health Research Center, San Diego, California.
6. J. Peters, Brain Behavior Laboratory, Simon Fraser University, Vancouver, British Columbia, Canada.
7. D. S. Ruchkin, Departments of Physiology and Computer Science, School of Medicine, University of Maryland, Baltimore, Maryland.

Some of the material covered in the correspondence was later amplified and presented at the conference; such material has been omitted. Other portions of the correspondence have been abridged and at times paraphrased for brevity and proper transition.

Weinberg: The development of circulated correspondence concerning alternatives to signal averaging implies that there are limitations to this technique. Vigorous use of signal averaging over the past ten years, I believe, has made one thing evident: the obfuscation of relationships between independent and dependent variables.

Let me offer these questions as keys to subjects that I hope we can develop further through correspondence and conversation: What is meant by "signal"? Is there really "noise" in the nervous system? What constitutes the stimulus? Is it defined by characteristics of the input or by its measurable influence on the nervous system? Is the nature of the signal in signal-to-noise ratios dependent on methods for detecting that signal? Is the electrode an uncontrolled averaging system? Precisely what information is lost through signal summation? Can the logic of signal averaging be extended so as to extract the signal related to the common element in variations of stimulus input, e.g., if we average the signals to different stimuli, all of which fall into the same abstract category, do we have a signal reflecting that abstraction? Can changes in the variability of a signal, given a stable mean, also be considered a signal, i.e., a proper response of the nervous system? Can spatially disparated signals be averaged to extract the common elements? Are the methods underlying topographic representations of voltage gradients methods of spatial averaging? These are questions that arise in consideration of signal averaging techniques. There are other obvious questions that arise in consideration of other techniques. For example, do Fourier transforms reveal anything about when something is happening as distinct from what happens? In pattern recognition techniques, how is the pattern to be detected determined in the first place?

Naitoh (as amplified below) suggested that, for the purpose of discussion, a distinction be made between signal extraction techniques and statistical techniques designed to establish whether signals are "real" or are different from other signals. This distinction raises questions in my own mind, especially when dealing with procedures like discriminant analysis. The methods of extraction are themselves statistical treatments of the data, the results of which are statements of the probability of the occurrence of the signal in relation to concommitant variability.

I have separated the techniques into two lists, the distinction between which may itself be a topic for discussion:

1. Extraction procedures: averaged evoked potentials, median evoked potentials, cross

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correlation techniques. Wiener filtering, averaging by cluster, spectral analysis using Fourier transforms, toposcopic and topographic representations, recursive filters.

2. Statistical procedures: multiple regression analysis, discriminant analysis, factor analysis, multiple and partial coherence and phase analysis, ANOVA and MANOVA approaches.

These are only partial lists; I offer them only as something with which we can begin.

Naitoh: I feel that two aspects of any evoked potential (EP) research must be discussed: (1) how are the EPs to be extracted and what measures are to be chosen for their analysis, and (2) what sorts of statistics are to be used on the EPs once they have been distinguished from the noise? Sometimes a distinction between mathematics required to extract EPs and mathematics required to evaluate them is indeed fuzzy (e.g., stepwise multiple discriminant analysis). But such a distinction is critical.

For amplification and discussion, I would like to present two lists, neither of which I consider comprehensive. First, methods of extracting EPs:

1. Median evoked potentials.
2. Pattern recognition with cross correlation.
3. Recurrence frequency function.
4. A *posteriori* Wiener filtering – This method may be well suited for developing an EP template as it gives, insofar as possible, a background-EEG free EP.
5. Sayer's phase-forcing method – This method is an extension of time-series analysis. It is well suited for single-trial analysis and also for detecting very small EPs.
6. Averaging by cluster (Saltzberg method).

Secondly, methods of statistically analyzing the features of EPs:

1. Stepwise multiple regression analysis.
2. Stepwise multiple discriminant analysis.
3. Hotelling's T^2 or Mahalanobis' D^2 – These methods have a limited scope of applications but are very instructive to those concerned with multivariate statistics.
4. Factor analysis, including discriminant principal component analysis.
5. Walsh analysis.
6. Basis function analysis – This is an analysis of EP on the basis of a few biologically "meaningful" wavelets.
7. Equipotential mapping (analogous to toposcopical analysis).
8. Multiple, partial, and pairwise coherence and phase analysis.
9. Information matrix – Multidimensional or simple Markovian.
10. ANOVA and MANOVA approaches.

Weinberg: I would like to consider further, specifically, the question of whether spatially disparate signals can be meaningfully averaged as an index of the commonality of the signals occurring at different sites. There is no obvious reason why the logic of the averaging could not be applied to the averaging of spatially disparate signals: after all, there is no more reason to believe that signals recorded from the same site on successive occurences of an input have commonalities. In a sense, the same question arises with regard to the averaging of signals ostensibly recorded from the same site in different subjects. Or to push the logic of signal averaging to its extreme, consider this: If it is true that an event-related potential indexes the attributes of the input, and if different signals from different inputs (stimuli) are averaged, then the resulting signal should be that associated with the commonality of the inputs, a commonality that could presumably be an abstraction, i.e., not associated with the absolute properties of the stimuli but with the relative properties of the stimuli.

But why average? Why obscure differences in the signal when those differences could be critical for an understanding of how different sites respond to input? To answer that signal averaging extracts the common signal from background noise is, I believe, unsatisfactory because current techniques allow us to identify the signal in single occurrences.

Gerbrandt: My first reaction to Weinberg's question as to whether signals that are spatially disparate can be averaged for the purpose of extracting the common element was another question: How can one distinguish between the multiple events that are superimposed onto the same space and time? Theta rhythms have usually been thought of as homogeneous events and as a functional entity. Studies now indicate that theta rhythms arise from multiple origins within the hippocampus (Gerbrandt et al. 1974, Winson 1974, Bland et al. 1975) and that some of these sources are independently manipulated by specific experimental variables (Gerbrandt et al.

1975). Thus, the many interpretations of *the* function of theta rhythms may have arisen because theta rhythms are of heterogeneous functional origin. The only thing that theta rhythms may have in common is their periodicity; the close phase coupling may merely be a device needed to preserve functional independence of circuitry (analogous to multiplexing) through a process of phase encoding.

Similarly, many disagreements have arisen over the proper distribution and function of motor potentials (MPs) in humans (Vaughan et al. 1968, Deecke et al. 1969, Gerbrandt et al. 1973) and many of these differences in result and interpretation seem to have resulted from the superimposition or multiple MP components (Gerbrandt 1974). Thus, any activity that occurs with an abrupt negativity around the time of a movement can be called N2, although it could be a change in the lateralization of Nl, a new command potential, or reafference mistakenly thought to be occuring before EMG onset. CNV-like events and the P300 wave, once thought to be functional entities called the "expectancy wave" and the "uncertainty wave" are now breaking down into a myriad of distributions, each affected by different experimental variables (Gerbrandt 1977, Ritter et al. 1974). Studies of single-unit activities during the readiness potential period indicate that different types of unit activity occur simultaneously under the same readiness potential, and changes in unit activity associated with changes in directions of movement are not reflected in the readiness potential (Tanji and Evarts 1976).

It may be then that the extraction of a common element from spatially disparate slow potential signals (even when they are recorded by a single microelectrode) represents nothing more than the fortuitous artifact of hundreds of parallel elements happening to statistically have only one phenotypic property in common – voltage rather than function. The following analogy may help to explain the issue: Imagine we search for the event-related sounds of a typical picnic. Would the sound of the picnic basket opening, the table cloth unfolding, and the ants chewing be termed a "common element," or is a picnic a complex enough happening to result in hundreds of independently generated sounds that nonrandomly summate into the typical picnic spectrogram?

Naitoh: Another fundamental question will be related to the EPs tie with basic neurophysiology and with behavioural psychology. For such applications, it may be necessary to consider changing correlational values as the time frame of observation is extended to days, or even months.

The fundamental question for time-series analysis of brain waves in general is whether the researcher believes the statement, "God plays dice." If God plays dice, all records will be noisy in one sense or another. For a given noise, a set of rules that the noise follows is developed. Later, the rules define the signal. If God does not play dice, there is somewhere in this world a pure signal, a deterministic event, a nonfuzzy thing. Only sadly our vision is blurred so that we cannot see this signal. Thus, in terms of signal analysis, there is always noise in the nervous system. Some may define it simply as "unwanted event"; others may consider that noise is all we get. In psychophysiology, "stimulus" is defined from both standpoints by referring to stimulus specificity and response specificity, i. e., a given stimulus produces the responses that are unique to the stimulus.

Herning: The signal-noise model of signal averaging has been a useful procedure for the extraction of signal buried in noise, but may not have been that useful in understanding the dynamics of cortical processing in humans. A reason for this is the concept of noise in the signal averaging framework.

I propose that a distinction be made between extraction noise (i.e., noise that a given statistical or extraction technique cannot explain) and meaningful biological noise (i.e., noise that is inherent in the physiology of the organism from which one is recording). Extraction noise in signal averaging is the part of the brain response that is averaged out. This noise may or may not be meaningful biological noise or perhaps may be part of a dynamically changing signal. Extraction noise in the use of autoregressive model-fitting in the detection of single-trial event-related potentials (ERPs) is the variance not accounted for when a model is being fit to the background EEG. In this case, the extraction noise is only that part of the background EEG not fit by the stochastic model. Since autoregressive model fitting in this example is modeling background EEG activity and signal averaging is largely ignoring background EEG activity, extraction noise has different meaning for each technique. Thus the quantification of extraction noise may be specific to the extraction or statistical technique used. Meaningful biological noise, on the other hand, is actual noise in the nervous system and the physiology of the organism, such as EMG, EOG, or other brain activity that is not related to the process under study. This noise may obscure the brain activity one is attempting to record.

Signal averaging, by its nature, has been a multiple-occurrence technique. That is, signal averaging requires a number of single trials or epochs to extract the signal or experimenter-meaningful part of the brain's response. Since a number of single-trial ERP extraction techniques have already been developed, an important question is whether the brain response to the same set of external events, say in a given CNV paradigm, is similar from trial to trial. My experience with the use of autoregressive model building techniques and stepwise discriminant analysis in the detection of auditory EPs is that the event-related cortical response may not be completely similar from trial to trial and its detectability is closely related to the nature of the on-going EEG activity at the time of the stimulus.

CNVs, motor potentials, P300s, and other slow electrical potentials would seem to be ideal for study with single-trial techniques since they occur over longer periods of time than pure sensory evoked responses and since they are sometimes observable in the raw EEG record. However, since these slow potentials have been deemed to represent more complex cortical processing, they may be more variable from trial to trial.

As with signal averaging, some alternate extraction or statistical techniques are also multiple-occurrence techniques and may be subject to some of the same criticisms as signal averaging. Such techniques include multiple regression, ANOVA, MANOVA, factor analysis, and discriminant analysis. Although these techniques can actually be used to classify or extract single-trial ERPs, more information is required than a single epoch of EEG data. For example, stepwise discriminant analysis (SWDA) and cross-correlation detection methods must build their classification rule or template from a number of single trials. In addition, the SWDA is not sensitive to latency changes in single ERPs. Other methods, like Wiener filtering and autoregressive model fitting, require EEG data from only a single epoch to extract or detect ERPs. These techniques are not as yet as sensitive as a multiple-occurrence technique. Certainly more research in this area is needed.

Ruchkin: Evoked potentials can usually be characterized as consisting of the sum of a response, sychronized with the stimulating event that elicits it, plus ongoing, spontaneous neuroelectric activity that is not related to the stimulus event. For data processing purposes, the event-related activity may be referred to as "signal" and the spontaneous activity as "noise."

There are many sources of variability of ERPs. At the single-cell level, there may be random fluctuations in membrane potentials, sometimes causing stray action potentials. Presumably, these neuroelectric events are due to random variations in metabolic and other such activity and may not be directly related to conscious or subconscious (e.g., autonomic, reflexive) information processing. It appears reasonable to call such activity noise since: (1) It may interfere with recording of signal activity. (2) The occurrence of random events such as stray action potentials could interfere with information processing by the central nervous system, and probably the CNS functions in a manner that will attenuate such random effects.

External events elicit a sequence of neuronal activity that may be reflected by ERPs. It appears reasonable to call this activity signal since: (1) It is not entirely random and, to some extent, can be brought under the control of the experimenter. (2) It may be related to other observations concerning the behavior and state of the subject. Of course, there are many types of CNS signals that we try to attenuate or tend to ignore because they are not readily related to external events.

There are difficulties with the definitions presented above. For example, from the point of view of an experimenter observing ERPs, ongoing autonomic neuroelectric activity is interference, but from the point of view of the CNS, it is signal. The problem is that the brain is a multiprocessor and only limited means are available for distinguishing the activities of the various subsystems.

As another example, trial-by-trial alterations in the state of the subject that affect ERP generation may be viewed as the source of either signal or noise. If the experimenter wishes to attenuate the effects of such alterations and can neither sufficiently control the state of the subject nor correlate the ERP fluctuations with behavioral observations, then the ERP fluctuatuons effectively amount to noise. However, if the experimenter is interested in analysing the ERP fluctuations and/or it is possible to relate the fluctuations to alterations in the behavioral state of the subject, then they can be viewed as signal. In effect, one man's signal may be another man's noise.

When the state of the subject cannot be determined by direct report, the problem of changes in state is difficult to deal with, and interpretations of results can be murky. Various *ad hoc* approaches have been devised; however, they are not guaranteed to always yield correct results. They work best when there is preliminay information available concerning the character of the data. For examples: (1) There may be reason to believe that the shape of the waveform is constant, but its latency varies. In this case, latency-compensated averaging or recognition index procedures might be used. (2) There are a limited number of states of interest and data are available that allow initial averages to be computed for each state. In this case, discriminant procedures may be used to classify the data prior to averaging.

Gerbrandt: Weinberg raised the question: "In pattern recognition techniques, how is the pattern to be detected determined" and what can it be used for? In my first dealings with such techniques, I developed a theta detector to quantify the records of theta rhythms in the rat. I then used the detector to synchronize computer averages of theta rhythms (ATRs) at a given electrode site. The resulting waveforms are analogous to averaged evoked potentials. By synchronizing to theta rhythms at a given electrode site and concurrently averaging ATRs at other electrode sites, measures of the average phase, frequency, and amplitude can be derived (Gerbrandt et al. 1974. Green et al. 1960).

In subsequent investigation of phase shifts between ATRs, I learned more about the advantages of the ATR and the distortions it is subject to (Gerbrandt et al. 1974, Lesevre et al. 1967, Ruchkin 1971). Some of the problems encountered could be large enough to result in unreliable averages, but they could be corrected by a program that sorts single trials on the basis of frequency modes and modes of amplitude heterogeneity. Analogous programs for sorting on the basis of amplitude heterogeneity have been developed (Ruchkin 1971, John et al. 1973). When frequency modulation is a problem, it can be corrected by scaling all events to the same frequency. Analogous programs have been developed to minimize amplitude and waveform distortions due to latency jitter (Woody 1967, Ruchkin 1974).

I then began wondering what else could be done with endogenous event-related potentials (EERPs). The possibilities are numerous and seem to break into three categories.

First, EERPs can be studied as primary dependent variables. Once the pattern recognition scheme is developed for the endogenous event, it can be averaged into EERPs by "auto-triggering" (where the triggering event is itself formed into an EERP) and related to concurrent EERPs at other electrode sites. For example, I have studied the topographic distributions of theta rhythms (Gerbrandt et al. 1974) and how they are affected by relevant experimental variables (Gerbrandt et al. 1975). Similar work has been reported for the human alpha rhythm (Magnus and Ponsen 1965, Remond et al. 1969). Less well defined electrical patterns, such as seizure spikes, the CNV, or P300, could also serve as templates that auto-trigger EERP averages of themselves and concurrent events at other electrode sites whenever cross correlations rise about a criterion. This technology is already in use (Woody 1967, Ruchkin 1974). Even unknown waveshapes can be extracted by searching for a highly correlated waveshape that is common to a set of data samples, using the waveshape as a first-level template for auto-triggering EERPs, then using the auto-triggered EERPs as second-level templates, etc. (Woody and Nahvi 1973). When the detected events are sudden enough in onset, duration, or off-set, such as is the case with seizure spikes, single-unit activity, or spindle bursts, the events can serve merely to synchronize EERPs in order to topographically search for clues about their anatomical and physiological origins. I term these potentials "trigger-referenced EERPs." Examples in the literature are the cerebral motor potentials, trigger-referenced to EMG onset (Vaughan et al. 1968, Deecke et al. 1969, Gerbrandt 1974). By extending the average backwards as well as forwards in time from the trigger event, possible causal relations can be found between the activities represented by EERPs and the trigger reference.

In the second category of EERP studies, the detected event is also synchronized to exogenous trigger, and the detection process is used to correct distortions in amplitude and waveshape that occur due to latency jitter in relationship to the exogenous trigger. This technique has been used for early (Woody and Brozek 1969) and late (Ruchkin 1974) components of the average evoked response. It should be used more frequently in EP studies to assure that changes in amplitude as a function of independent variables are not just artifacts of latency jitter.

In the third category of EERP studies, EERPs are secondary data that can be used as probes or state variables that affect primary events such as average EPs, single-unit activity, or other types of EERPs. The timing relationship of the background state (EERP) may or may not be considered. A number of studies have shown, for example, that the phase of occipital alpha rhythms is important in determining the waveshape and amplitude of the visual EP (Magnus and Ponsen 1965, Remond and Lesevre 1967, Peacock 1970). Walter (1968) has suggested that background delta activity may be an important determinant of CNV amplitude. The possibility also exists that some components of EPs are just artifacts of background states (EERPs) that are superimposed upon the EP under certain conditions (Peacock 1970). Clearly, EERPs are going to be in widespread use in the field of EP research, although they are in limited use at present.

Peters: To separate an evoked response (signal) from the ongoing background EEG (noise), the two are generally subjected to the signal averaging process, the theory being that the random noise that is not time-locked to the stimulus will average to zero, leaving only the signal. Unfortunately, the averaging process does not provide any information with respect to trial-to-trial variability of the waveforms. This information can be obtained by simultaneously calculating the variance and standard deviation along with the average (Walter 1972). However, once obtained, the variance gives no indication of whether the variability is in the noise or the signal, and if in the signal whether it is due to amplitude or latency changes.

The first possibility, that the variability might be due to noise, has been examined by filtering each trial with a brick-wall digital low-pass filter prior to calculating the average and SD. The filtering did not significantly affect either the average or SD during the CNV interval. The evoked responses (particularly to S1) were altered by the last filter, which cut off all activity above 4 Hz. This would seem to support the contention that the increased variability seen following S1 is not due specifically to noise. On this basis, one could speculate that if the pre-S variability is taken as a baseline, then increments in variability beyond that level might be due to signal alone. This cannot, however, be taken as fact based on this limited data.

Given that the above hypothesis does hold up, the data still say nothing about whether the variability is one of amplitude or latency. This question might possibly be addressed by examining the variability of the amplitude over time as opposed to at a specific point in time. Specifically, given N data points and the average amplitude and SD associated with each, an average of both amplitude and SD over, say, the first 10 points results in what is often referred to as mean amplitude and the mean SD associated with it. If, in addition, the SD of the average and SD are calculated, one is conceivably dealing with amplitude changes over time. The applicability of this calculation to latency variability is presently being investigated.

A third point of interest is the minimal change induced in the CNV by selectively filtering single trials prior to averaging. Although this did not significantly affect SD, the reduction in noise associated with the average may significantly reduce measurement errors. The most frequently used measures of CNV magnitude have been peak amplitude to a visually smoothed curve, area, and mean amplitude in some interval (say 100 to 200 msec) prior to S2 (Peters et al. 1976), all of which have been chosen primarily for their reduction in error due to the ongoing EEG associated with the average. If prefiltering can reduce this noise still further without altering CNV morphology and/or amplitude, then measurement accuracy should improve.

This discussion is only a preliminary review of the analysis that is currently being pursued. The possibilities discussed here must be compared to single-trial analysis before any final statement may be made.

Weinberg: Let me raise one other more specific issue – the question of whether topography can give us information about responsiveness to input, i.e., can it extract signals from the EEG. The greatest weakness of topography has been its inability to easily represent topographic relationships as they occur over time. At least two dimensions must be reserved for designation of site, and a third for the dependent variable, usually voltage, leaving the fourth dimension, time, dangling. It seems to me that if there were some simple method of reducing four-dimensional information accumulated with topography into an easily digestible two-or even three-dimensional display, this technique would tremendously enhance our understanding of the total pattern of activity within the brain that is responsive to input.

One way in which this might be done is to use correlations for the purpose of collapsing two dimensions. What topography attempts to do is describe the spatial change in voltages over a two- or three-dimensional surface by extrapolating voltage gradients from observed voltages distributed in space, and the relationship of the gradient changes to time. Specifically, what is meant by "relationships"? In this context, the term refers to the ways in which voltages in different parts of the brain covary. And this can be determined through correlations. But correlations between what? It is very difficult, if possible, to correlate everything with everything else and still retain a simple picture of relationships.

A partial solution is to identify an arbitrary standard within the brain, such as vertex change in response to an input, which is then correlated with activity from numerous other sites. Once a standard is selected, the question can be asked: What is the degree to which activities in different parts of the brain differ with respect to the standard? These correlations would be an index of the relationship between the activity recorded from different sites in the brain, all of which are compared to the same standard. This pattern can then be displayed as changing correlations over time and plotted on a two-dimensional surface representative of the array of electrodes, using the Z axis for time. This should work nicely for the changes that occur after a signal, for some given small period of time, but it is not a satisfactory arrangement for the observation of long-term changes in a spontaneous record. Nevertheless, when used for changes occurring after known inputs, on successive occasions, the correlations plotted with techniques of back-suppression, at multiple sites, give a kind of topological representation of voltage relationships occurring over widespread areas of the brain.

MULTIVARIATE ANALYSIS OF EVENT-RELATED POTENTIAL DATA: A TUTORIAL REVIEW

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Introduction

Purpose

This review is concerned with the choice among techniques that can be used to analyze data acquired in studies of event-related potentials (ERPs). Many analysis procedures are available, and their appropriateness has been a matter of some dispute (Donchin 1969, 1976; Vaughan 1974; John et al. 1978). Yet no technique is inherently good or bad. Techniques exist to extract information from data, and the choice depends on the degree to which any given technique makes the data informative. Data yield information when they can be made to reduce uncertainties that investigators have with respect to specific questions. The choice of an analysis technique depends, therefore, on the experimental questions and on the data.

This review describes several of the available ERP data analysis procedures within a consistent framework. Focus is on the application of multivariate statistical techniques. Many investigators are apprehensive of multivariate procedures even when such techniques are particularly appropriate. Through an intuitive rather than formal development, we hope to demonstrate the motivation for multivariate approaches to ERP data analysis (for a more rigorous presentation, see Glaser and Ruchkin 1976). Our purpose is to show that multivariate techniques are a natural and logical extension of the more commonly employed univariate techniques.

Most, if not all, data analysis techniques that have been applied to ERPs can be described as *linear combinations;* the diversity of approaches masks an underlying common structure. Making this structure explicit should facilitate meaningful comparisons between techniques and provide a heuristic for selecting the techniques best suited for different experimental problems.

The ERP as a vector

Fig. 1 presents four hypothetical ERP waveforms. Each waveform is simply the sequence of voltages recorded at each of the time points. In the example, there are 15 such measurements for each waveform. Thus, a waveform is represented by an ordered set of numbers $[x(1,j), x(2,j), \ldots, x(i,j), \ldots, x(P,j)]$, where j identifies the ERP, and $i=1, \ldots, P$ indexes the time points. These primary data vectors (recall that an ordered set of numbers is called a vector) are the average ERPs computed from the EEG segments recorded during each trial of an experiment. Average ERPs can be arranged in a data matrix, as shown in Fig. 1, where rows represent the ERPs. There will be one row-vector for each combination of values of the independent variables in the experiment. The columns represent the time points. The measurements at each time point are the primary dependent variables in the study. Thus, there are as many dependent variables as there are time points. The number of variables depends, therefore, on the sampling rate used during digitizing. It is this many-dependent-variable situation that compels consideration of multivariate statistical techniques (Tatsuoka 1971, Donchin 1966).

The data matrices generated in ERP experiments are fairly large. When the data from all subjects for several electrode positions are accumulated over several experimental conditions and replications, a matrix with many hundreds of rows is created. If single-trial vectors are considered, the matrices are gargantuan.

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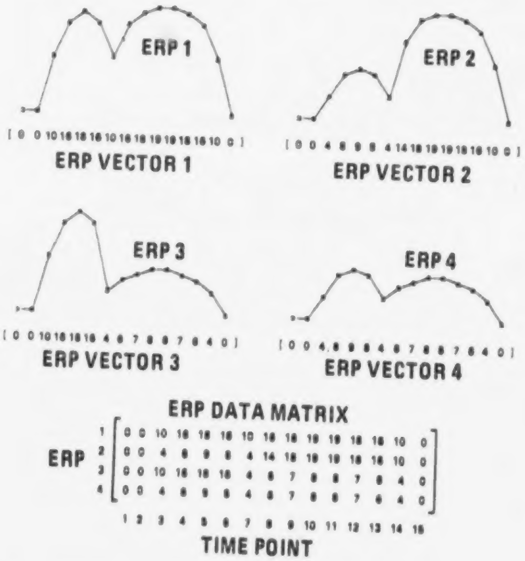

Fig. 1. Four simulated average ERPs are shown along with their corresponding vector representations. Below the ERPs, the vectors have been grouped into the average ERP data matrix.

While number of rows in the matrix is determined by experimental design and cannot be reduced, the number of columns may well be reducible since the time points in themselves are not of primary interest. Rather, ERP studies tend to focus on the behavior of derived dependent variables called *components.* The term component, which will appear frequently in the following discussion, is used to describe the elementary processes of which the ERP is presumably constructed (see Donchin et al., 1978, for a discussion of this concept). The number of components is generally much smaller than the number of time points. Each component therefore affects the values measured at many time points, and at each point one may measure the contribution of many components. The measurements over different time points are, then, not independent. Furthermore, if it were possible to measure the contribution of each component to each time point, then it would be possible to express the measures of each component as a single value that combines the component's contribution at the appropriate points. The number of columns in the data matrix could thereby be reduced to the number of components.

This has, in fact, been standard operating procedure in the ERP laboratory. Investigators combine the elements of the data vectors to yield one value per component. The combination rules are quite diverse, but most can be described as linear combinations.

Linear combinations

A linear combination of the elements of a vector is formed quite simply. For a vector with P elements, a set of P coefficients is required, each one corresponding to one point in the vector. Forming a linear combination involves two steps (Fig. 2). First, each data value x(i), i=1, . . ., P, is multiplied by the corresponding coefficient a(i). Then these products are summed to yield the linear combination y(1). A different linear combination of the same data points x(1) through x(P) can be obtained with a different set of coefficients b(1) through b(P), producing a new value y(2), as shown in Fig. 2.

$$[X_1\ X_2\ X_3\ \ldots\ X_P] \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ \vdots \\ a_P \end{bmatrix} = Y_1$$

$$[\text{ERP ROW VECTOR}] \times \begin{bmatrix} \text{COEFFICIENT} \\ \text{VECTOR} \end{bmatrix} = \begin{matrix} \text{COMPOSITE} \\ \text{VARIABLE} \end{matrix}$$

$$(X_1a_1) + (X_2a_2) + (X_3a_3) + \ldots + (X_Pa_P) = Y_1$$
$$(X_1b_1) + (X_2b_2) + (X_3b_3) + \ldots + (X_Pb_P) = Y_2$$

Fig. 2. The elements of the ERP vector are linearly combined to yield a composite variable. The value at each time point is weighted by the corresponding coefficient, and the products are summed.

The number of possible linear combinations of any vector is unlimited, as there are infinitely many coefficient vectors with which to form linear combinations. Thus, each of the different coefficient vectors in the coefficient matrix in Fig. 3, when applied to the data matrix, yields a different linear combination. The rules for determining which coefficients to use, given a data matrix, define a method of data analysis. In other words, for each set of rules used to develop a coefficient matrix, there is a corresponding method for data analysis. The techniques can, therefore, be evaluated by comparing the manner in which they generate the coefficients.

Note that *data analysis* in this context refers to a method of measurement rather than to a procedure for decision-making or hypothesis-testing. The linear combinations yield values (measures) that are then

$$\text{ERP}\begin{array}{c}1\\ \\ \\ M\end{array}\begin{bmatrix}X_{11} & X_{12} & X_{13} & \cdots & X_{1P}\\ X_{21} & X_{22} & X_{23} & \cdots & X_{2P}\\ & & & & \\ X_{M1} & X_{M2} & X_{M3} & \cdots & X_{MP}\end{bmatrix}_{\substack{1 \qquad\qquad P\\ \text{POINT}}} \begin{array}{c}1\\ \\ \\ \\ P\end{array}\begin{bmatrix}a_{11} & \cdots & a_{1N}\\ a_{21} & \cdots & a_{2N}\\ a_{31} & \cdots & a_{3N}\\ & & \\ a_{P1} & \cdots & a_{PN}\end{bmatrix}_{\substack{1 \qquad N\\ \text{COMBINATION}}} = \text{ERP}\begin{array}{c}1\\ \\ \\ M\end{array}\begin{bmatrix}Y_{11} & \cdots & Y_{1N}\\ Y_{21} & \cdots & Y_{2N}\\ & & \\ Y_{M1} & \cdots & Y_{MN}\end{bmatrix}_{\substack{1 \qquad N\\ \text{COMBINATION}}}$$

$$[\text{ERP DATA MATRIX}] \times \begin{bmatrix}\text{COEFFICIENT}\\ \text{MATRIX}\end{bmatrix} = \begin{bmatrix}\text{COMPOSITE}\\ \text{VARIABLES}\end{bmatrix}$$

Fig. 3. The process of forming a linear combination of a single ERP is generalized to the case where N linear combinations are computed for each of the M ERPs from an experiment.

used for inferential purposes. There will be an interaction between the inferential intent of the investigator and the measurement he chooses to use. One purpose of this paper is to elucidate these interactions.

In the remainder of the paper, four analysis techniques are described, two traditional (peak and area measures) and two multivariate (principal components and discriminant analysis). In each case, the rules that determine the coefficients that define the analysis and then its advantages and disadvantages are discussed. An intuitive understanding of these rules should enable an investigator to determine which techniques are appropriate given the nature of the data and the questions addressed by the research.

Analysis techniques

Peak analysis

Peak measurement is probably the simplest approach to quantification of differences in amplitude of ERP components. A peak is defined either as the largest or the smallest voltage value in an interval representing the latency range of the component being measured. The measured values are expressed either as the difference between successive peaks (e.g., N100-P300) or as the difference between the peak and the average of several points (e.g., N100-baseline).

Peak measurement can be easily expressed as a linear combination. We begin with a time function extending over an epoch. First, we select a time segment in the epoch so that only values x(K) through x(L) are considered. Next, the maximum (or minimum) value x(M) is found between points K and L. The coefficient a(M) for the point at the peak is set to one. All other coefficients are set equal to zero. Forming a linear combination with these coefficients is clearly equivalent to peak measurement. Fig. 4 illustrates measurement of the two peaks for the ERP from Fig. 1. The peak measurements may then be subjected to an analysis of variance to test for significant differences across experimental treatments. We do not, of course, imply that this paragraph describes the actual procedure used by an investigator executing a peak analysis. We do assert that whatever procedure is used in practice, it can be described formally as a linear combination.

Peak analysis, like all techniques, should be evaluated in terms of the nature of ERP data. First, peak analysis assumes that it is not necessary to measure more than a single point to adequately quantify the magnitude of a component. This assumption restricts its applicability, as discussed below. Furthermore, because peak measurement includes contributions from all components that affect the voltage at a time point, the investigator may in fact be measuring effects due to components other than the one he believes accounts for the peak.

The principal advantage of peak measurement is its face validity. It is intuitively appealing. The method is a direct analog of the visual inspection procedure for gaining impressions of data trends. Moreover, it is almost the only measure that is easy to obtain from x-y plots. Many investigations are restricted to this method, as it requires nothing but an x-y plotter, a ruler, and enough time for this rather tedious job. An additional advantage is that the magnitude measurements are fairly independent of differences in latencies of components across ERPs.

The technique has several disadvantages. It is not easy to avoid experimenter bias in identifying a peak,

$$\text{ERP}\begin{bmatrix}0&0&10&16&18&16&10&16&18&19&19&18&16&10&0\\ 0&0&4&8&9&8&4&14&18&19&18&18&16&10&0\\ 0&0&10&16&18&16&4&6&7&8&8&7&6&4&0\\ 0&0&4&8&9&8&4&6&7&8&8&7&6&4&0\end{bmatrix}_{\text{TIME POINT}} \begin{bmatrix}0&0\\0&0\\0&0\\0&0\\1&0\\0&0\\0&0\\0&0\\0&0\\0&1\\0&0\\0&0\\0&0\\0&0\\0&0\end{bmatrix}_{\text{PEAK}} = \begin{bmatrix}18&19\\9&19\\18&8\\9&8\end{bmatrix}_{\text{PEAK}}$$

$$[\text{ERP DATA MATRIX}] \times \begin{bmatrix}\text{COEFFICIENT}\\ \text{MATRIX}\end{bmatrix} = \begin{bmatrix}\text{PEAK}\\ \text{MATRIX}\end{bmatrix}$$

Fig. 4. Peak measurements are made for the ERPs illustrated in Fig. 1.

because waveforms are often not as sharply delineated as in idealized examples. Also, it is often difficult to define a baseline or reference peak in the data, particularly when there are few trials in an average or when rapid oscillations are superimposed on slow potentials that begin during the baseline period and continue throughout the epoch (Squires et al. 1977). (Baselines will be discussed later.) Another problem appears when several peaks are measured in the same waveform. These peaks are often not independent, and the application of inference techniques that assume independence may be inappropriate. Component overlap presents a serious problem in peak measurement. A typical example is the effect that the "slow wave" (Squires et al. 1977) has on the measurement of P300 amplitude. A similar vexing problem is the dissociation of ERP components from contingent negative variation (CNV) (Donchin et al. 1975). Fig. 5 illustrates a case in which a slower component accounts for differences in another component measured by the base-to-peak method. Unfortunately, such relationships, while probably prevalent, are not always so clear in real data.

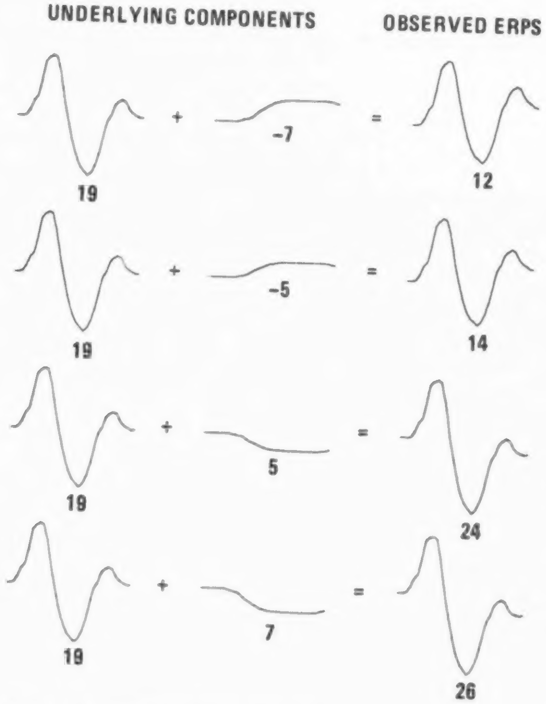

Fig. 5. Baseline-to-peak measurements are made for ERPs composed of two underlying components: a constant biphasic waveform and a varying slow process. The numbers represent peak values relative to the initial baseline (arbitrary units). The measures on the observed ERPs suggest that the sharp positive (downward) component varies across the four ERPs when in fact it is constant.

The peak measurement technique suffers from other limitations. Because the measurements are based on a single point, moderate amounts of nonsystematic variance can obscure real differences. Further, peak measurement is not very applicable when measuring slow potentials such as the CNV or readiness potential (RP). Finally, peak amplitudes reveal nothing about the waveshape of the component being measured.

It should be noted that, despite its apparent simplicity, peak measurement presents challenging problems in statistical estimation. The waveforms are rarely smooth and the precise latency at which the component achieves a maximum cannot often be defined unequivocally. The relative order of magnitude of different peaks may well be preserved even when the errors of measurement are large. However, when these measurements are used to define the latency of components, the uncertainty in peak definition may lead to serious difficulties. Other techniques have been used to identify peaks (e.g., locating the intersection of the tangents of positive and negative slopes). Whatever the solution, the investigator should avoid seduction by the deceptive simplicity of the measures.

In summary, peak measurement techniques are most applicable when the data analyst is dealing with distinct components exhibiting clear differences in ERP records. Peak analysis was probably an adequate approach for the earlier, exploratory phase of ERP research when large, dramatic effects were sought. In general, the procedure will be valid when the processes underlying the ERP are well understood or possibly when the experiment is unidimensional in scope (e.g., when stimulus intensity is the only variable). Peak analysis is limited in scope when the investigator is attempting to dissect complex ERPs, especially when components overlap.

Area measures

The measurement of the area under selected portions of the ERP curve is similiar to peak analysis. Areas are computed by integrating the voltages, relative to a reference baseline. Limits can be set so that the interval encompasses either an entire component or some portion of it. The area is also a linear combination of the ERP. The first step is to select a range of points K through L that correspond to the duration of the component or subprocess being studied. The coefficients for points K through L are then set to one; all other coefficients are set to zero. A baseline interval is chosen for reference. Computation of areas by linear combination for the four sample ERPs of Fig. 1 is illustrated in Fig. 6.

Area analysis is based upon specific assumptions about the data. Unlike peak measurement, area analysis is based on the premise that the amplitude of a component is accurately gauged by combining values

$$\text{ERP}\begin{bmatrix} 0&0&10&16&18&16&10&16&18&19&19&18&16&10&0\\ 0&0&4&8&9&8&4&14&18&19&19&18&16&10&0\\ 0&0&10&16&18&16&4&6&7&8&8&7&6&4&0\\ 0&0&4&8&9&8&4&6&7&8&8&7&6&4&0 \end{bmatrix}_{\text{TIME POINT}} \begin{bmatrix} 0&0\\0&0\\1&0\\1&0\\1&0\\1&0\\1&1\\0&1\\0&1\\0&1\\0&1\\0&1\\0&1\\0&1\\0&0 \end{bmatrix}_{\text{AREA}} = \begin{bmatrix} 70&126\\33&118\\64&50\\33&50 \end{bmatrix}_{\text{AREA}}$$

$$[\text{ERP DATA MATRIX}] \times \begin{bmatrix}\text{COEFFICIENT}\\ \text{MATRIX}\end{bmatrix} = \begin{bmatrix}\text{AREA}\\ \text{MATRIX}\end{bmatrix}$$

Fig. 6. Area measurements are made for the four ERPs from Fig. 1. Each area is a linear combination of the corresponding ERP vector.

measured at several time points. If the analyst chooses an appropriate interval, then it is likely that most of the contribution of the component to the total ERP will be included. Unfortunately, this measurement procedure does not deal adequately with component overlap. As the area limits are extended, the probability increases that contributions from other components will be included.

Area measurement offers many of the advantages of the peak methods. The technique is easy to understand and involves relatively little computation, although a ruler and x-y plotter no longer suffice. In addition, some degree of latency jitter can be tolerated, provided the area limits are appropriately adjusted. Areas are more accurate representations of the magnitude of slow components than are peak measures. Also, they are less susceptible to random variations if enough time points are included in the interval.

Area measures share many of the disadvantages of peak methods. Determination of integration limits is often difficult, or even arbitrary, because components cannot be accurately resolved by visual inspection. Component overlap and intercorrelation can be serious problems, and such complications may be very difficult to identify. As with peak detection, the technique is sensitive to the definition of the baseline. Finally, the procedure yields no information about component waveshape.

In summary, whenever the investigator is analyzing ERPs with independent, well-defined components and clearly defined baselines, area measurement is valid. However, when component overlap is suspected, or when a more detailed analysis of the waveform is needed, then one of several multivariate techniques might yield better results.

Principal component analysis (PCA)

Component overlap: At this point, it will be instructive to review the nature of linear combinations for peak and area component measures. Peak analysis implies that the magnitude of a component can be adequately represented by the peak value of the corresponding wave. Thus it assigns a coefficient equal to 1.0 to the time point at which the wave shows a maximal deflection (coefficient vector A in Fig. 7). For area measures, the assumption is that the sum of values over an interval characterizes component magnitude. These points are given equal weight by assigning 1.0 to their coefficients (vector B in Fig. 7). Weighting these points equally over the interval K through L results in incorporating an undetermined contribution of the magnitude of adjacent or overlapping components into the measure. The greater the component overlap, the more serious the problem. Clearly, it would be preferable to weight the values in the ERP in proportion to the contribution the component of interest makes to the variance at each time point. The contribution at each point is determined by the component's waveshape. Such a set of weights is represented by vector C in Fig. 7. Coefficients are highest in the region of the ERP where the amplitude is determined to the greatest extent by Component II. In the region where Components I and II have the greatest degree of overlap, the weights are small, reflecting the assumption that Component II accounts for only a part of the amplitude variation in this interval.

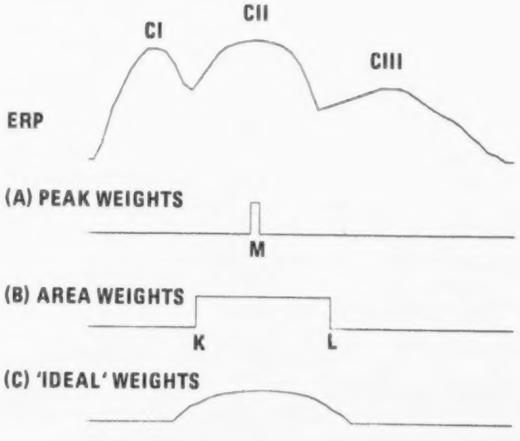

Fig 7. Three coefficient vectors for measuring Component II are represented graphically.

Principal component analysis (PCA), followed by an analytic rotation, is one procedure for obtaining such a set of weights. The pattern of covariation among data points within an ERP is used in determining the coefficients. PCA is a technique for extracting a small number of components, each representing systematic influences on many time points, from the total variance in the ERP data matrix.

Example: two-dimensional ERPs: If measurements at two points are correlated, it is likely that they are influenced by a common process. For example, the values of individual points constituting an ERP component tend to increase and decrease together, or covary, as the magnitude of the component is modulated. This suggests that the matrix of covariances between time points might serve as a basis for determining ERP components. If a number of adjacent time points exhibit high covariance, an ERP component can be assumed to be influencing them jointly. Patterns in the covariance matrix are complicated by component overlap, but if two overlapping components are not highly correlated across all experimental variables and electrode sites, then principal components and associated techniques should be successful in separating them.

A few examples may help in visualizing the relationship between variance, covariance, and principal components. Each example will involve a set of average ERPs, each made up of only two time points, x(1) and x(2), representing the peak amplitudes of the components. These ERPs can be represented by two-element vectors consisting of values for the variables x(1) and x(2). We can plot the ERPs in a two-dimensional space with x(1) as the abcissa. In the first example (Fig. 8a), x(1) is the value at a time point strongly influenced by an underlying ERP component, while x(2) is a time point from a part of the sampling epoch not influenced by that component. The variance within these waveforms, as represented in our two-element vectors, occurs almost entirely along axis X1. Points x(1) and x(2) exhibit little covariance. If we are interested in a measure of Component I in any given waveform, then it suffices to measure the value along X1. Thus, the variances and covariances show that the component varies along X1, and further, that X1 is the only axis (or time point) the component influences. We can use this information to derive a measure of the magnitude of the component in any given waveform, which in this case is simply the value along the X1 axis.

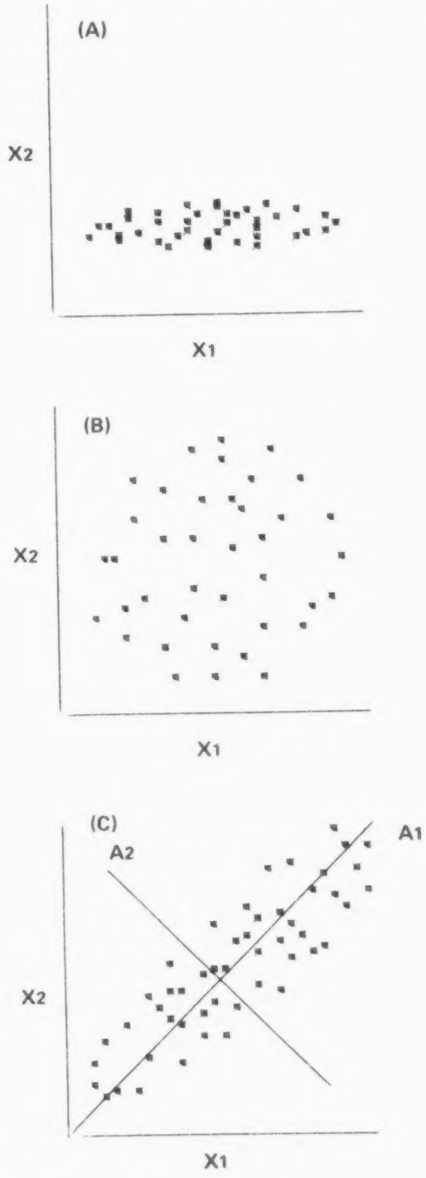

Fig. 8. Scatter plots represent measurements at two points along an ERP. (a) ERP varies a great deal at point x(1) but is relatively constant at x(2). (b) Variance is present at both points, but x(1) and x(2) are unrelated. (c) Both x(1) and x(2) are unrelated. (c) Both x(1) and x(2) vary. In addition, the two variables exhibit strong covariance. Axis A1 is the dimension of maximum variability. Axis A2 is orthogonal to A1.

In the second example, x(1) and x(2) are affected by independently varying components (Fig. 8b). In this case, there is considerable variance along both X1 and X2, and so neither variable alone characterizes the total variance in the data matrix. Further, these two variables do not covary, i.e., the value of x(1) is not systematically related to the value at x(2). Two separate components can be assumed to influence the ERPs. If, for any given waveform, we wish to assess the magnitude of Component I, then X1 provides the appropriate measure, and we can ignore the variance along X2. Similarly, Component II is measured along X2. Thus, we have two independent components, one identified with X1, the other with X2.

The third example illustrates the case that motivates the use of PCA and rotation techniques in ERP research. In this example, x(1) and x(2) are affected by the same underlying component. Both variables exhibit a considerable amount of variance. However, because they are influenced by a common process, or ERP component, they covary quite strongly, as revealed by the elongated diagonal scatter plot in Fig. 8c. Although the two variables are not perfectly correlated, there is substantial common variance. The imperfect correlation may occur because one or both of the points are affected by other components or because noise and error cannot be completely eliminated. As we sample two points at shorter and shorter temporal intervals, the correlation between them will increase.

If there is only one process, then it would be convenient to find the axis along which it can be measured, as X1 was used in the example in Fig. 8a. *This is a crucial point:* one component is to be considered as a single dimension, although its existence is manifest at many time points. At each time point, that portion of the variance that is influenced by the single ERP component is extracted. The maximum variability occurs along A1 as in Fig. 8c rather than along X1 or X2 as in Fig. 8a, although A1 is determined by both axes. By examining the relationship of A1 to the two original axes, the component's influence at each of the time points can be determined. Furthermore, a measure of the component can be obtained for each ERP by projecting the data points from the two-dimensional time-point space onto the A1 axis in the new component space.

There are two different ways to characterize the data in terms of A1. The new axis can be more or less "like" either of the original axes. A useful measure of the similarity, or association, between the derived axis and each of the original axes is the cosine of the angle between the original and the derived axes. There are, of course, as many such angles for each derived axis as there are original axes. The cosines of these angles, which are equivalent to correlation coefficients, are called *component loadings* in PCA jargon. A loading is therefore a measure of the association between the principal component and the original axes, and for each principal component there are as many loadings as there were original axes. There is, also, for each of the ERPs in the data-base a measure that expresses its value on the axis A1. This measure is called a *component score.* For each principal component, there are as many component loadings as there were original axes (time points) and as many component scores as there were observed ERPs. In this context, we are no longer interested in values at time points but rather in components of variance. Therefore, a new space spanned by the derived components rather than by the time points is developed. Each component will be represented by an axis in the component space. Amplitudes can then be measured along A1 just as they were with X1 in Fig. 8a. These measurements are represented by the component scores.

While A1 accounts for most of the variance in the data, there may remain a significant percentage of variance still to be explained. This can be viewed by observing the *residuals,* or the representations of each ERP after the influence of A1 is removed from the original data. It is possible to obtain a second axis A2 that meets the criteria that (1) it accounts for the largest possible percentage of the residual variance, and (2) it is orthogonal to A1. There will then be two new axes for the ERP data, each accounting for an orthogonal source of variance in the data. Note that in the example the variance along A2 does not represent a second ERP component. Rather this variance reflects the variability in the two time points that is not due to Component I.

Extensions to multidimensional data: For two-dimensional data, the process is thereby exhausted. If the original data are multidimensional, however, the process can continue, successively adding orthogonal axes. The number of axes can theoretically be equal to the number of dimensions, i.e., the number of digitized voltages in the sampling epoch. However, in practice, due to the large measure of correlation between data points, the percentage of variance accounted for by successive principal components diminishes rapidly. For ERP data, most of the variance is accounted for by six to eight components (Donchin 1966, Donchin et al. 1975, Squires et al. 1977).

The result of this procedure is a representation of each ERP in a space that might have five or six dimensions as opposed to the raw ERP space that had P dimensions, where P may be quite large (as 50 to 250 time points are typically measured). The value along each new axis for each ERP (i.e., the component score) is a linear combination of the original P points. The principal components of variability among points are determined by analyzing patterns of covariation, and the relative contribution of each component to each of the original ERPs can then be assessed.

A complete PCA involves at least four major steps. First, the P x P variance-covariance matrix is computed. Second, the principal components are extracted from this matrix. This produces a component matrix showing the loading, or influence, of the principal components at each time point. The loadings matrix will have one row for each principal component and one column for each time point. Another way to think of the weights is as hypothetical basic ERP components. Because these basic ERP components tend to be somewhat correlated across observed ERPs, and also because time points within each electrode often covary, it is usually the case that principal components exhibit weights across the entire epoch. In order to remedy this undesirable situation, an additional step is performed. A Varimax rotation (Kaiser 1958) is performed as a third step to better derive the basic ERP components from the loadings matrix. The Varimax procedure has the effect of maximizing high loadings and minimizing low ones while maintaining orthogonality. The result in practice is to concentrate the high loadings for each component to a restricted region of the epoch, thereby producing distinct basic ERP components.

The fourth stage locates each observed ERP in the new, reduced, rotated space. The transformation is accomplished by multiplying each observed ERP vector by a coefficient vector derived from the rotated loading vector for each component output from the Varimax step. The component loadings, which reflect the association between each time point and each particular component, are used to develop the coefficients needed to form linear combinations. Each raw ERP vector yields a composite score representing a measure of the magnitude of a specific component in a specific ERP. If M principal components were retained and rotated by the Varimax procedure, then to each ERP there would correspond M such linear combinations. These measurements can then be subjected to an analysis of variance to test for significant differences across experimental treatments.

Principal components as linear combinations: Before examining the assumptions and restrictions of PCA, as described, it is appropriate to relate PCA to the discussion of coefficients, illustrated in Fig. 7. The objective of PCA is to produce a set of weights for each component that will permit assessment of the contribution of each component to amplitude variance of each point in the ERPs. The linear combination of raw ERP time points to form composite scores for each component for the ERPs is represented in Fig. 9. The raw ERPs (Fig. 1), now listed as deviations from the grand mean, are given. The weights were determined by a PCA of the covariance matrix for these waveforms followed by a Varimax rotation.[2]

$$\text{ERP}\underset{\text{TIME POINT}}{\begin{bmatrix} 0.0 & 0.0 & 3.0 & 4.0 & 4.5 & 4.0 & 4.5 & 5.5 & 5.5 & 5.5 & 5.5 & 5.5 & 5.0 & 3.0 & 0.0 \\ 0.0 & 0.0 & -3.0 & -4.0 & -4.5 & -4.0 & -1.5 & 3.5 & 5.5 & 5.5 & 5.5 & 5.5 & 5.0 & 3.0 & 0.0 \\ 0.0 & 0.0 & 3.0 & 4.0 & 4.5 & 4.0 & -1.5 & -4.5 & -5.5 & -5.5 & -5.5 & -5.5 & -5.0 & -3.0 & 0.0 \\ 0.0 & 0.0 & -3.0 & -4.0 & -4.5 & -4.0 & -1.5 & -4.5 & -5.5 & -5.5 & -5.5 & -5.5 & -5.0 & -3.0 & 0.0 \end{bmatrix}} \underset{\text{COMPONENT}}{\begin{bmatrix} .00 & .00 \\ .00 & .00 \\ -.00 & .06 \\ -.00 & .08 \\ -.00 & .07 \\ -.00 & .06 \\ .01 & .02 \\ .03 & .01 \\ .03 & -.00 \\ .03 & -.00 \\ .03 & -.00 \\ .03 & -.00 \\ .03 & -.00 \\ .02 & -.00 \\ .00 & .00 \end{bmatrix}} = \underset{\text{COMPONENT}}{\begin{bmatrix} 1.0 & 1.0 \\ 1.0 & -1.0 \\ -1.0 & 1.0 \\ -1.0 & -1.0 \end{bmatrix}}$$

$$[\text{ERP DATA MATRIX}] \times \begin{bmatrix} \text{PCA} \\ \text{COEFFICIENT} \\ \text{MATRIX} \end{bmatrix} = \begin{bmatrix} \text{COMPONENT} \\ \text{SCORES} \end{bmatrix}$$

Fig. 9. Component measurements for the ERPs from Fig. 1 are made using the PCA-Varimax method. The grand mean ERP has been subtracted from each raw ERP before the covariance matrix was factored. Note that coefficients are maximal in the region where a particular component dominates.

The result of the linear combination is a matrix of component scores, as shown in the right of Fig. 9.

As noted briefly above, the nature of the numbers yielded by PCA and their role in data analysis must be understood. The analysis yields two sets of values: the coefficients (i.e., the component loadings) required for forming the linear combinations and the actual linear combinations (i.e., the component scores) computed for specific ERPs. In practice, use is often made of the set of component loadings used in computing the coefficients. These loadings, a set of which is available for each component, represent a measure of the association of each time point with each component. For ERP data, the loadings obtained after a Varimax rotation tend to be large over restricted regions of the epoch and small elsewhere. This suggests that the principal components can be identified with underlying ERP components. A separate set of principal component loadings will be extracted for each independently varying ERP component.

To illustrate these concepts, the ERPs displayed in Fig. 1, and the ERPs labeled "observed ERPs" in Fig. 5 were subjected to PCA. In Fig. 10a, the component loadings from PCA of Fig. 1 ERPs are plotted. Because the two ERP components varied independently, two principal components were extracted. Only one component was extracted from the Fig. 5 ERPs (Fig. 10b). Note that this set of loadings represents the influence of the second "underlying component,"

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[2] Each of the four waveforms was replicated 20 times, with independent uniform random noise (−0.01, +0.01) added to each point in order to avoid computational difficulties. The arithmetic precision of the computations is greater than indicated by the figures.

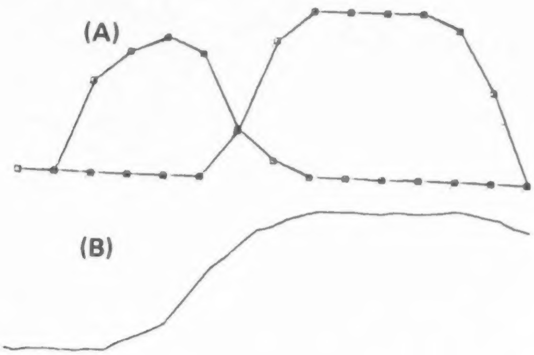

Fig. 10. Component loadings. (a) Component loading vectors from PCA of the waveforms presented in Fig. 1 are plotted. (b) the single principal component vector from PCA of the 'observed ERPs' in Fig. 5 is illustrated.

The PCA did not extract a component corresponding to the first "underlying component" because this component did not vary across ERPs. It is notable that even though visual inspection suggests that the waveforms in Fig. 5 differ in their peak-to-peak amplitudes, the PCA correctly extracted the underlying "slow component."

Fig. 11 presents plots of loadings obtained in several different experiments. In each case, the "reference" ERP is the grand mean ERP obtained by averaging across all subjects, all electrodes, and all experimental conditions. It is clear that, despite the diversity of the experiments, the PCAs reveal a remarkably uniform structure for the ERP components.

While PCA identifies systematic sources of variance in the data, it is not necessary that these sources correspond to the experimental manipulations of interest to the investigator. This correspondence must be established by analyzing the linear combinations, or component scores. It is these linear combinations that are most clearly analogous to the base-to-peak measure discussed previously. It is often true that some components are, and some are not, affected by experimental variables. Thus, for example, Squires et al. (1977) found that components corresponding to P300 (component 2 in Fig. 11a) are affected by the probability that the eliciting stimulus will appear. Similar plausible relationships were established for other poststimulus components. On the other hand, component 4 in Fig. 11c, while accounting for 12% of the total variance, was not affected by any experimental manipulation, and represents such factors as differences in baseline levels between subjects and between electrodes.

It is very important to note that components revealed by PCA depend on the variance in the data. Some part of this variance is induced by the experimental manipulations. For example, some of the structures of Fig. 11 are restricted to the region immediately following a stimulus. Others show a component that corresponds either to the CNV or to P300 appearing between stimuli. In Fig. 11a and b, only one component appears in this region. Fig. 11c shows two components in the same range because experimental manipulations generated two sources of variation in the same time region.

Several assumptions underlie application of PCA to ERP data. First, it is important to note that the principal components model is a linear model. In other words, it is assumed that individual ERP components do not interact; i.e., they simply sum together to produce the complex ERP waveform.

Second, the analysis assumes that the major sources of variance are orthogonal. In most cases, independent manipulation of ERP components of interest will be characteristic of a good experimental design. In addition, the different scalp topographies of components will enhance their independence. Nevertheless, there will be cases in which two underlying ERP components are highly correlated across experimental variables and electrodes. In such cases, PCA will produce a loading vector and component scores based on the compound waveform. Therefore, it is not always possible to equate a principal component with a specific deflection in the ERP. Therefore, PCA is not a magic and foolproof way of analyzing experimental data. It is a tool that must be used in conjunction with good design based on a plausible theoretical approach. However, examination of the loadings matrix will reveal the nature of the principal components. Independence does not necessarily imply orthogonality, but it has been our experience (as shown in Fig. 11) that an orthogonal model can satisfactorily represent many data bases. Further, techniques are available for examining the assumption of orthogonality (Harman 1960, Mulaik 1972). To produce a nonorthogonal solution, the analyst follows the principal components extraction with an oblique rotation instead of the orthogonal Varimax rotation.

Third, component variability is assumed to be in the amplitude rather than in the time domain. There might be considerable difference in the time at which a component peaks so that the amplitude at a given time point varies because of latency rather than "real" amplitude differences. The principal components technique will extract a component associated with this latency-based amplitude variability, as illustrated in Fig. 12. In this example, latency variability of a

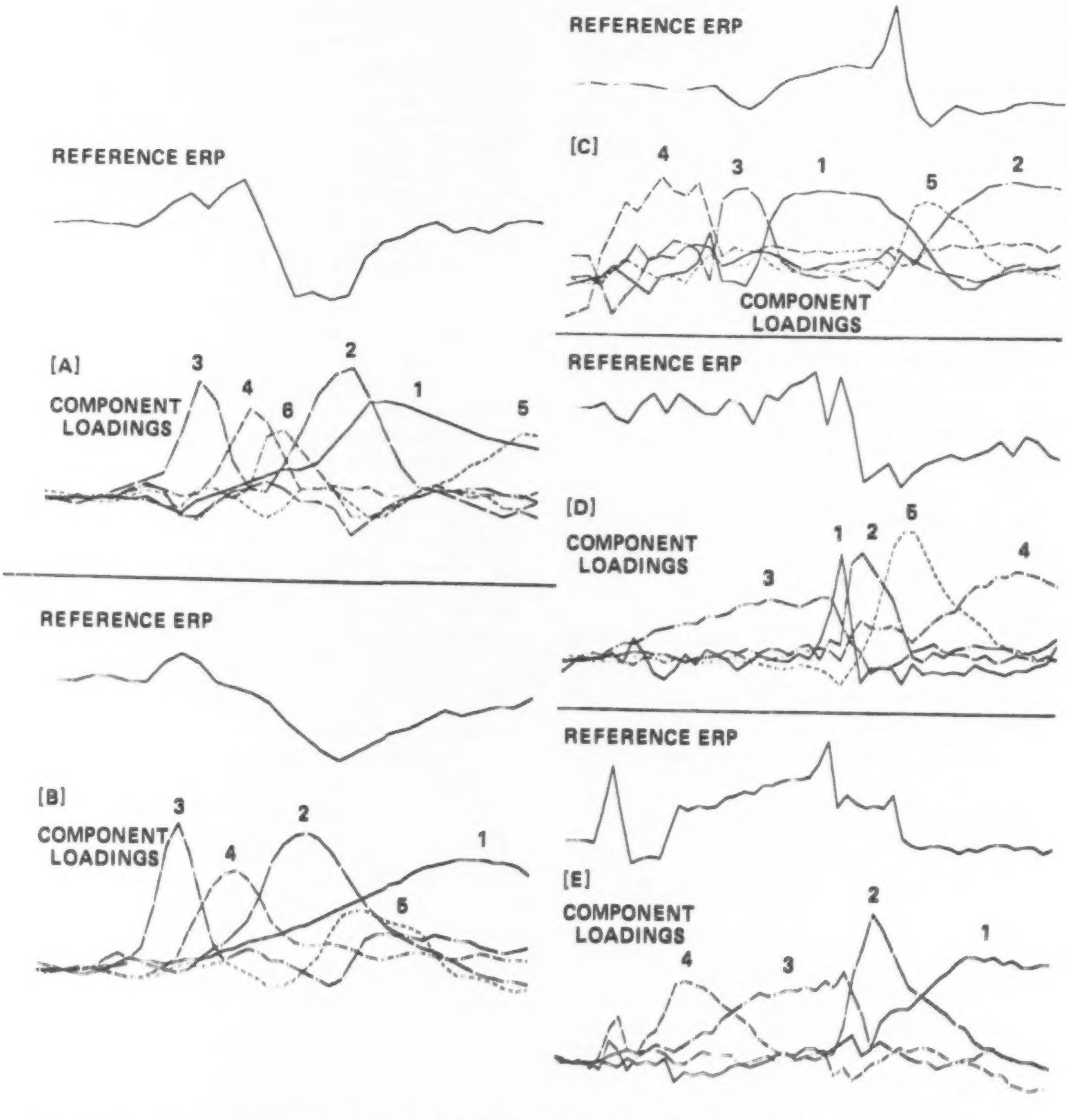

Fig. 11. Component loadings and reference ERPs from P300, CNV, and RP studies. (a) Squires et al. 1977, (b) Duncan-Johnson and Donchin 1977, (c) Donchin et al. 1975, (d) McCarthy and Donchin 1976, (e) McCarthy and Donchin, in press.

constant-amplitude ERP component produces a loading vector that is nonzero in the entire range over which the component varies. Its biphasic form results from the fact that the waveform in the right segment of each ERP is above the grand mean but in the left segment it is below the mean. As the example demonstrates, neither the component nor the variance of its amplitude will be adequately represented. Unfortunately, PCA will not discriminate between variance due to latency changes and true magnitude differences. Careful examination of average ERPs, however, should make such effects apparent. If latency variability is evident, then an adaptive filtering algorithm proposed by Woody (1967) might be applied to adjust the latencies of components before the PCA is done (Ruchkin and Glaser, this section; Kutas et al. 1977).

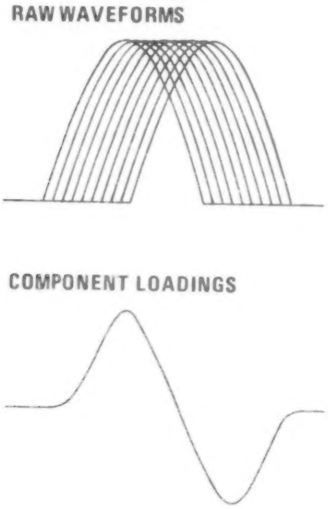

Fig. 12. Raw waveforms for component with fixed amplitude that varies in latency across observations and the component loadings resulting from PCA of the data.[3]

Association matrix selection: In the foregoing discussion, the principal components were assumed to have been extracted from a covariance matrix. Covariance, however, is one of many possible indices of association that might be computed between two variables. Correspondingly, a PCA might be applied to different association matrices. Thus the data analyst must choose among association matrices before performing the PCA. Most PCA programs allow a convenient choice among the *mean crossproduct, covariance,* and *correlation* matrices. The consequences of this choice are substantial, as it affects both the component loadings and the component scores that will emerge from the analysis.

Each matrix is obtained by applying a different transformation to the data prior to the computation of the association index. These transformations are illustrated in the three scatter plots in Fig. 13. The two-point "ERPs" plotted are similar to those shown in Fig. 8. The raw ERPs are plotted in Fig. 13a as points in two dimensional space. The points define a swarm that has a specific locus in the space, depending on the means of the two variables. The extent of the swarm along each axis depends on the variance of the data in each dimension. Association indices measure the degree to which knowledge of one of the two variables provides information about the other. The mean crossproducts (Fig. 13a) are formed by summing the results of cross multiplication of the values of x(1) and x(2) for all observations. No transformation is performed on the raw data. The covariance (Fig. 13b) is computed in a similar manner except that the mean value of each variable is subtracted from each observation before forming the crossproducts. In ERP terms, this implies that the grand-mean ERP is subtracted from each average ERP vector prior to the computation of covariances between corresponding ERP points. The effect is to move the data swarm within the two-dimensional space so that it is centered on the origin. For the correlation matrix (Fig. 13c), the correlation coefficient is obtained by standardizing each variable so that all variables have an equal variance prior to the formation of the crossproducts. The mean of each variable is subtracted from the values of the variable, and the resulting differences are divided by the standard deviation of the variable. After these two transformations of the data in Fig. 13a, the data are centered on the origin and all dimensions have an equal variance.

The effects of these transformations on the result of a PCA are quite complex. A proper understanding of these effects must guide the choice of the association matrix to which the PCA is applied. Of principal importance is the fact that the substrate in the PCA analysis is the variance of the analyzed data. The total variance of the raw data is analyzed when the mean crossproducts are used. Part of this total variance derives from the differences between the means of the different variables. This portion of the variance is removed in computing the covariance matrix. Another portion of the variance is contributed by the differences between the variances of the individual variables. This source is removed upon computation of the correlation coefficient. Quite different variances are factored, then, when a PCA is applied to each of the three matrices.

That the mean is not removed from the data in a crossproducts analysis has at least two effects on the results of a PCA. First, portions of the ERP that have a large base-to-peak amplitude will emerge as components even when they are not affected by the experimental variables. Second, in most cases the loadings of the first component extracted in such an analysis roughly duplicate the waveform of the grand-mean ERP.

Analysis of the covariance matrix will yield principal components that correspond to the variance around the grand-mean ERP. The extent to which the individual ERPs differ from the grand mean, rather

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[3] Input consisted of a fixed-amplitude half-sine wave replicated 20 times at each of 10 different latencies. Independent uniform random noise (-0.01, +0.01) was added to each point in order to avoid computational difficulties. The arithmetic precision of the computations is greater than indicated by the figure.

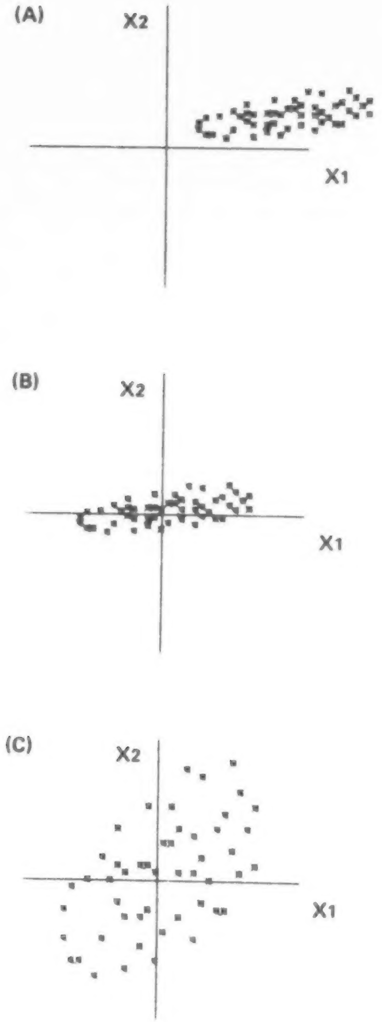

Fig. 13. Scatter plots representing two points along an ERP. (a) Computation of mean crossproducts requires no transformation of these raw data. (b) ERPs after the transformation necessary for covariance computation has been applied. Note the grand mean for the ERPs is now (0,0). (c) Transformations involved in correlation computation have been applied to the ERPs. The grand mean has been subtracted, and each point has been divided by its standard deviation across ERPs. The scale along the axis is now in standard deviation units, unlike the raw measurement scales for (a) and (b).

than the absolute amplitude of the different ERPs, will determine which components will be extracted. Analysis of the correlation matrix will usually yield components of a similar nature, except that the loadings will be more uniform across the extent of a component rather than reflect the component waveshape. Thus, time points at which differences are small, and possibly unreliable, can receive large loadings due to the standardization of values at each time point.

These considerations must be kept in mind when interpreting the component scores obtained from PCAs applied to the different matrices. Of particular importance are the implications to the interpretation of the "polarity" of the scores. Only for a cross-products analysis will a negative factor score be a sure indication of the polarity of the corresponding component in the original ERP. In a covariance analysis, the score for a given ERP component represents its amplitude relative to the grand mean. For example, a positive peak lower in amplitude than the corresponding peak in the grand mean will have a negative component score.

In general, PCA of covariance matrices is most useful in ERP experiments. The data analyst is interested only in those ERP components that are affected by the experimental manipulations. The differences between ERPs relative to the grand mean are of prime interest. Furthermore, since the values at all time points represent voltage, they all have identical scales, and therefore there is no need to scale the data by the standard deviations. The covariance matrix is therefore preferable to the correlation matrix.

Advantages and disadvantages: PCA provides information about the amplitude variability and waveshape of components. The technique also provides valuable information when components overlap, provided they are not highly correlated. Given a set of measures on the orthogonal principal components, the analyst can then employ an analysis of variance to assess the effects of experimental variables on the independent components. An important feature of this method is its adequacy regardless of ERP component waveform. It handles fast and slow components equally well. Another advantage is the existence of a well-developed statistical theory to guide the data analyst. Finally, though this procedure requires a substantial amount of computation, it is possible to quickly summarize results from complex experiments that yield hundreds of individual ERPs.

As usual, there are also disadvantages to the method. The power and nature of the technique may not be intuitively obvious, nor is it immediately clear how the conclusions of visual inspection are translated into numerical values by PCA. A more serious disadvantage is that PCA confounds latency and amplitude variability. The results should therefore be interpreted with great care whenever latency variability is substantial across ERPs. Finally, PCA requires significant computing power. While such procedures can be easily performed at most computer facilities, the requirements exceed the power of laboratory computers.

Discriminant analysis

Discriminant analysis is a classification procedure. Detailed treatment of its application to ERP data has been given by Donchin and Herning (1975) and Squires and Donchin (1976). It is similar to PCA in the sense that it provides yet another rule for developing a linear combination of the observations. The difference lies in the fact that in PCA the coefficients are obtained through an analysis of the total variance in the ERP data matrix, disregarding the independent variables that group the ERPs to produce component scores. In discriminant analysis it is assumed that the ERPs can be objectively classified into two or more groups that correspond to values of the experimental variables. Between-group variance of the ERPs is then analyzed directly. Again, a linear combination of each ERP vector in the data matrix is produced, but this time the linear combinations are selected to account for an increasing proportion of the between-group rather than the total variance.

The discriminant analysis strategy can be described with a simple example. Suppose a number of two-point, x(1) and x(2), ERPs are collected under two different levels of sunspot activity, high and low. The data points are plotted with different symbols for high and low sunspot ERPs (Fig. 14). Ignoring differentiation between data points and analyzing total variation, as in PCA, results in line Al accounting for maximum *total variance.* However, with the discriminant analysis procedure, which maximizes *between-groups variance,* the variance along A2 would be of interest. Each ERP can then be projected on this line. The next step would be to determine a criterion point along the line that runs through the group means.

Two-group discriminant analysis provides a set of coefficients for linear combination with the ERP vectors to produce a single composite variable that can then be evaluated against the discriminant criterion. The matrices involved are illustrated in Fig. 15. The example is based on the ERPs from Fig. 1. ERPs 1 and 3 (group A) are discriminated from ERPs 2 and 4 (group B). Stepwise discriminant analysis (Dixon 1975, Jennrich 1977) will use only a subset of the P time points in the ERP data matrix to construct a discriminant function. It will select variables (or time points) for inclusion such that the first variable selected accounts for the maximal proportion of the between-group variance, the second variable accounts for the maximal portion of that between-group variance that remained unaccounted for after the first step, and so on. This selection process continues until some specified condition is met. This condition can be the number of variables included, the amount of variance accounted for, or the point at which no improvement is observed in some criterion.

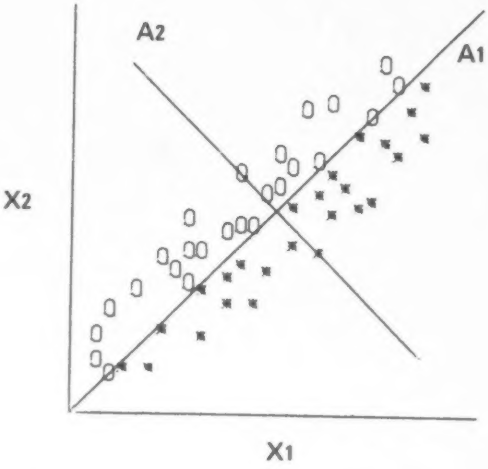

*Fig. 14. A scatter plot of two-point ERPs illustrates one of the differences between discriminant analysis and principal components analysis. Symbols * and 0 represent ERPs from two different groups. PCA would select A1 as the principal axis because maximal variance in the total data base occurs along this dimension. Discriminant analysis would select A2 as the primary dimension because it maximizes between group variance.*

The sources of between-group variance are independent, but in general will not be orthogonal. The *discriminant function* is simply a set of coefficients for selected time points. The *discriminant score* is the result of the application of the function to any ERP. Thus, the discriminant score is a sum of several weighted amplitudes along the ERP epoch plus a constant. Again, the essential similarity of the multi- and univariate techniques is evident. Discriminant analysis is a procedure for selecting time points at which the amplitudes are to be measured and for obtaining a relative weighting of these amplitudes. It does so by attempting to provide optimal separation between two groups of ERPs. So, it differs from the conventional base-to-peak measures merely in the way in which the amplitudes are selected for measurement.

$$
\begin{array}{c}
\text{ERP}\left[\begin{array}{ccccccccccccccc|c}
0 & 0 & 10 & 16 & 18 & 16 & 10 & 16 & 18 & 19 & 19 & 18 & 16 & 10 & 0 & 1 \\
0 & 0 & 4 & 8 & 9 & 8 & 4 & 14 & 18 & 19 & 19 & 18 & 16 & 10 & 0 & 1 \\
0 & 0 & 10 & 16 & 18 & 16 & 4 & 6 & 7 & 8 & 8 & 7 & 6 & 4 & 0 & 1 \\
0 & 0 & 4 & 8 & 9 & 8 & 4 & 6 & 7 & 8 & 8 & 7 & 6 & 4 & 0 & 1
\end{array}\right] \\
\text{TIME POINT}
\end{array}
\left[\begin{array}{r}
0.0 \\ 0.0 \\ 16.8 \\ 26.6 \\ 28.7 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ 0.0 \\ \hline -899.3
\end{array}\right]
=
\left[\begin{array}{r}
218.8 \\ 361.0 \\ 210.9 \\ 318.0
\end{array}\right]
$$

$$
\left[\begin{array}{c}\text{AUGMENTED} \\ \text{ERP DATA MATRIX}\end{array}\right] \times \left[\begin{array}{c}\text{DISCRIMINANT} \\ \text{FUNCTION}\end{array}\right] = \left[\begin{array}{c}\text{DISCRIMINANT} \\ \text{SCORE}\end{array}\right]
$$

Fig. 15. Discriminant analysis of the data from Fig. 1 is illustrated.[4] *ERPs 1 and 3 are discriminated from ERPs 2 and 4. A column of ones is added to the ERP data matrix so that the constant for the discriminant function is added to the combination of values at the time points. The constant appears at the bottom of the discriminant function vector. The discriminant analysis was limited to three points.*

Once the discriminant function has been computed, it can be employed in several ways. It can be applied to other sets of ERPs collected under the same general experimental paradigm. Besides group classification, the composite variable produced by the function can be used as a measure of ERP magnitude. This is particularly true when one of the data sets used to develop the function is characterized by a very small ERP (see Donchin and Herning 1975). The discriminant function thus defines a continuum along which the resemblance of an ERP to the average for one group or the other can be assessed. Discriminant analysis also identifies the regions of the ERPs that best differentiate between groups. The time points selected identify these regions and can serve as a guide to visual inspection.

Example of application: Squires and Donchin (1976) investigated the performance of stepwise discriminant analysis (SWDA) using single-trial ERPs elicited by auditory stimuli in an experiment designed to measure the effect of the *a priori* probability of stimuli on the magnitude of the P300 component. Two groups were used to develop the discriminant function. One contained ERPs associated with a rare event; the other contained ERPs associated with a frequent event. The SWDA program was able to classify correctly as "rare" or "frequent" 89% of the single trials (on the average) if information from multiple electrode sites was used. The data from all subjects were then pooled to generate a "subject-independent" discriminant function and used to classify data obtained from seven new subjects. These data thus served as a *training set* for development of the discriminant function. The subject-independent function proved sufficiently general to correctly classify 81% of the single trials from new subjects.

Examination of misclassified trials can be instructive. In Fig. 16 averages for incorrectly classified trials are shown with the averages for correctly classified trials for the two groups upon which the function was based. Trials on which the rare event (loud signal) was presented, but classified as frequent, actually evoked, on the average, an ERP characteristic of the response to frequent stimuli (soft signal). This result suggested that the ERP elicited by the stimulus does not depend entirely on the *a priori* probability of the stimulus. Subsequent work has shown that expectancies that depend on the precise structure of the stimulus series must be considered (Squires et al. 1976).

Advantages and disadvantages: SWDA objectively assesses ERP differences along any independent dimension, provided data can be obtained at points representing the extremes of the dimension. The power of the technique to extract differences makes it applicable to analysis of single-trial ERP data (Donchin 1969, Donchin and Herning 1975, Squires and Donchin 1976). Finally, there is a statistical theory that guides the interpretation of the statistics derived by the technique.

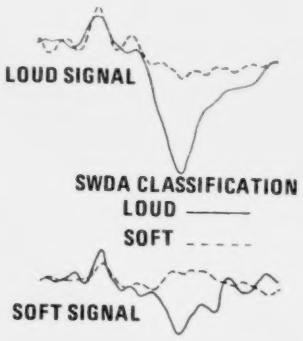

Fig. 16. Average ERP waveforms sorted according to stimulus presentation and discriminant analysis classification. Note the average ERP for misclassified loud (rare) stimuli exhibited no P300 and, therefore, resembled responses evoked by soft (frequent) stimuli.

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[4] The four waveforms were each replicated 25 times with independent uniform random noise [–2.0, +2.0] added to each point in order to avoid overflow/underflow computational errors.

There are several disadvantages to SWDA. The most obvious is the need to have an independent basis for grouping ERPs so that a discriminant function can be developed. If the coefficients are computed on a training set for later use on another ERP data base, then the analyst must be sure the ERPs for the two groups within the training set differ significantly. If the investigator is using discriminant analysis to test for differences between the groups upon which the function was built, then caution must be exercised, because the power of the technique may produce misleading results. It is possible that the analysis may differentiate between groups on the basis of random variation in the sample rather than systematic differences that might be present in the population (Lachin and Schachter 1974). We can be confident that the function yields a meaningful differentiation between groups when either the original sample is large or satisfactory classification is achieved when the function is applied to data not used in the training set.

The need for cross validation of the discriminant function must be emphasized. The discriminant analysis programs always yield a function. Even if the two groups in the training set are not different, the program will develop a rule for distinguishing between the groups, capitalizing on random distinctions between the groups. In general, the weakness of such a function will be apparent, since it will provide a very weak classification of the training set. However, it should never be assumed that a strong classification of the training set is sufficient to establish the quality of the discriminant function. The user must demonstrate the validity of the discriminant function. The most direct way for doing so is to apply the function to an altogether new set of data. This *test set* must consist of data that belong to one or the other of the classified groups. The function should classify the test set at least as well as it classifed the training set. If the test set is classified weakly (in the sense that a random classification would have done as well), the function is not providing a valid discrimination. This test requires, of course, that the analyst have sufficient data to generate a test set. On occasion this is not possible. In some cases there are barely sufficient data in the training set to develop the discriminant function. At least two procedures are available to test such limited data.

The *jackknife* (or *leave-one-out*) test uses the training set itself to generate a test set. It proceeds to compute a set of discriminant functions, each with one case removed from consideration. It then applies the discriminant function to the held-out case. A table is obtained in which each case is classified on the basis of a discriminant function computed without use of that particular case. This procedure is a fine check but should not be overrated. The effect that any given case has on the discriminant function is relatively weak, so the repeated computations of discriminant functions using the same data cannot but produce results that are very similar to those obtained by the original computation. Only if the within-group variance is very large (relative to the between-group variance) would the jackknife yield results that are very different from the original computation. Since the procedure is embedded in the packaged SWDA programs, there is no great cost in its use, and it may well give useful information, but it should be interpreted with great caution.

As an alternative to the jackknife test, a randomization test may be applied to the training set to assess the original discriminant function. In this procedure (for an example see Donchin and Herning 1975), the training set is used to generate two new groups by randomly assigning each case to one of the two groups, disregarding the original group membership. A discriminant function is then obtained for the randomly shuffled data. This procedure is repeated several times, and a distribution of discriminant functions is obtained. This distribution provides an estimate of the discriminant function that can be expected from the data set under purely random classification. If the original function falls within this range, it is probably invalid.

As with principal components analysis, the relationship of discriminant analysis to visual inspection may not be clear, although the investigator should be able to see the differences between waveforms in tracings. An additional disadvantage is the need to transfer the raw data to a reasonably large system for analysis. Once a discriminant function has been computed for an adequate training set, however, the computation of discriminant scores involves only a few multiplications and a summation which can easily be done on a small laboratory computer system or even a portable calculator.

Baseline in ERP analysis

The treatment of baseline in ERP research has always been a vexing problem. All amplitudes must be measured relative to some value. Peaks and areas are always determined with respect to a reference point. In PCA, subtraction of a baseline value from each ERP is necessary to reduce error variance. In fact, if the ERPs are not adjusted by preliminary baseline subtraction, the first extracted component will usually reflect the differences between the level of the individual waveforms. In discriminant analysis, baseline subtraction helps minimize within-group variance. Traditionally, the baseline has been defined as the average value over a portion of the recording epoch just preceding the stimulus that evoked the ERP. However, the assumption that this average represents a true "zero point" is sometimes untenable. Often there is too much variability in prestimulus baselines. Another problem is the presence of event-related activity in these intervals. The CNV and RP are common confounding factors. The problem of the fluctuating baseline is sometimes circumvented by measuring peak-to-peak rather than base-to-peak amplitudes. However, accurate interpretation of peak-to-peak measurements is dependent upon knowledge of the correlation between components and the degree to which components overlap.

The first problem to be faced, then, is determination of a reliable measure of the baseline. One possible solution is use of trimmed averages. The *midmean* has been used by Donchin et al. (1973). The midmean is obtained by eliminating all values in the upper and lower quartiles. The arithmetic mean of the remaining values is then computed. This measure is unaffected by extreme deviations in the data. Similar statistics are described by Tukey (1977).

The problem of one component overlapping or correlating with another must also be considered. PCA seems to offer the best approach to this problem. A plot of component loadings should make the degree of ERP component overlap clear. The loadings will also help reveal highly correlated ERP components. ERP components that covary strongly will appear within a single PCA loading vector. The ERP data analyst might also examine discriminant analysis results to determine whether a baseline is free of ERP activity. If points within the baseline interval contribute substantially to the discriminant function, then one must carefully check for the presence of ERP components in that portion of the epoch.

The problems associated with baseline determination in ERP data analysis should not be ignored. The consequences include missing significant differences in components because of variability in the baseline and incorrectly identifying the varying component because components overlap or are highly correlated.

Practical aspects of multivariate analysis

ERP investigators have been slow to adopt multivariate techniques, despite their advantages. To some extent, this reluctance may be due to a tradition determined by the nature of the instrumentation prevalent in this field. Special-purpose averagers with an x-y plotter as the major output device naturally lead to an emphasis on visual inspection. Even though more and more general-purpose computers are being used in ERP laboratories, there is a reluctance to venture beyond the confines of the laboratory. This section is meant to serve as a guide to transfer of data from the laboratory computer to a larger facility for analysis.

The large central computer facility offers several advantages over minicomputer systems for multivariate data analysis. One significant advantage is the availability of standard statistical packages such as BIOMED (Dixon 1975), SPSS (Nie et al. 1975), and SOUPAC (Dickman 1974). These packages tend to be adequately documented and relatively error free. Although such procedures as PCA and discriminant analysis could be performed on a minicomputer, their implementation is certainly not easy. Advanced programming skills are required to adapt programs that require large amounts of computer memory to the restricted program space of a minicomputer. Further, some knowledge of numerical analysis is required to ensure reasonably accurate computations. The result of all this effort may be a procedure that is impractical because it takes many hours to execute, depending upon the particular minicomputer. In general, resources are probably better spent in developing an efficient procedure for transferring data to a larger computer.

We have been able to process ERP data at a wide variety of computer facilities. In each case, all that is required is that the data be written on a standard "industry-compatible" digital magnetic tape. A typical specification is for a nine-track tape drive with a recording density of 800 or 1600 bits per inch. Such drives are readily available for all minicomputers. The cost is relatively high, but as we have noted elsewhere (Donchin and Heffley 1975), the lack of such a tape drive cripples the ability of the investigator to fully realize the advantages of computerizing a laboratory. The use of direct computer-to-computer communication is an alternative. It is possible to attach a laboratory computer to a central computing facility, an arrangement most often accomplished via telephone. At present, most of these lines permit relatively slow communication (300 baud) and the transfer of large data bases is, therefore, somewhat impractical.

Once a standard tape drive is available, ERP single trials and averages along with other psychophysiological or behavioral data can be written on digital tapes. If the tape drive is well aligned, then any data written on the tapes are, in principle, readable by any corresponding tape drive regardless of manufacturer. While the physical bit pattern recorded on a tape can be read with ease, different computers maintain different protocols for organizing data on tapes. The differences lie in such factors as the size and structure of data blocks and the codes used to represent numbers and characters. These factors are termed the *logical format* of the tape and are fairly independent of the physical recording method.

A comprehensive discussion of the logical formats used for digital magnetic tape is beyond the scope of this paper. However, some general information will be offered to help guide investigators who are not familiar with the details of data transfer between computer systems. First, data may be stored in either symbolic or binary formats. Symbolic format represents each data point as a series of characters as if the data were output on a line printer. Binary representation is direct output of data in the internal code of the computer. There is a tradeoff between the two representations. Data in symbolic format are more easily transferred from one computer to another because they are usually written using standard coding schemes (ASCII or EBCDIC) that almost all systems accept. Binary format usually requires special processing to handle differences in such characteristics as computer word size and number representation. The binary format is, however, more efficient. Binary representation requires less space on a tape and is faster because the conversion from internal code to characters is not needed. In general, it is practical to store the average ERPs from an experiment in symbolic format, but because of the volume of data, single trials are best stored in binary format.

Another factor is the format in which numbers are grouped into records, and sometimes blocks, on the tape. A problem arises because the command most readily available to the programmer, the FORTRAN "WRITE" statement, causes data to be output in a logical record format that is specific to the particular minicomputer and operating system. In addition, data output in this manner typically consume a great deal of tape, because a data array is usually broken apart and output in chunks of about 128 bytes with relatively large gaps between these records. Unfortunately, most minicomputer software systems do not offer the FORTRAN programmer commands to output an entire array (EEG channels by time points) as one record. Such commands are usually available within the operating system and so can be interfaced to the FORTRAN program via an assembly language subroutine call (Donchin and Heffley 1975). Using this strategy, data will be written on tape faster and more efficiently than with standard FORTRAN commands.

The user must then face the problems associated with reading data into the larger computer at the central computer facility. Resolving these problems will usually require three steps. First, data are read, at best one full array at a time, into the computer's memory. Second, for binary representation, conversion from the minicomputer to large computer numeric format is done. If the data are stored on tape as integers, rather than as real numbers, then this step involves simply extending the sign bits, assuming two's-complement arithmetic. Third, data can then be output to a storage device on the large computer from which they can be read by any of the analysis programs available on the system.

Several major statistical packages are available for multivariate analysis. It is not worthwhile in this context to recommend one package over the others. Each has its advantages and disadvantages. In most computing centers, the statistical consulting staff tends to favor one or another package for reasons that have more to do with the history and training of the staff than with rational considerations. Users are wise to use whichever package receives maximal support at their installations. (It is possible, of course, to write a PCA, or any other multivariate program, by utilizing any of the readily available mathematical, or matrix manipulation, subroutine packages such as SSP or IMSL.) An unfortunate characteristic of most packages, with the exception of SOUPAC, is that none includes a convenient routine for performing a *repeated-measures analysis of variance* (ANOVA). It so happens that most ERP experiments require such a design, since the comparisons are usually within subjects and across experimental conditions; i.e., each subject is tested repeatedly in all experimental conditions. The error terms in such an ANOVA are quite different from those used in standard designs (see Keppel 1973). One ought to avoid using between-subject variance as the error term. It is important, therefore, to have a repeated-measures ANOVA program that can analyze the factor scores yielded by the PCA. Of the three large statistical packages, BIOMED, SPSS and SOUPAC, only SOUPAC offers a repeated-measures ANOVA program. In our own laboratory, the package called ALICE (Walker et al. 1976) has proven useful for this purpose.[5]

Summary

We have reviewed four different techniques for the analysis of ERP data (peak and area measurement and principal component and discriminant analysis) and indicated that all four involve the formation of linear combinations of ERP amplitudes at selected time points. The techniques differ with regard to the manner in which the time points are selected and to the coefficients that are used to scale the voltages as they enter into the amplitude measure. The strategy adopted in each technique makes it more or less appropriate for any given ERP problem.

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[5] ALICE can be obtained from its developers (ALICE Associates, 29 Wellesley Avenue, Natick, Massachusetts 01760). Versions for several computer systems are available.

Conventional procedures determine the selection of time points largely through visual inspection of records. Components are identified, more often than not, by inspection, and then peak amplitudes or areas are measured. Multivariate procedures derive the measures through an analysis of either total or between-group variance in the data acquired in any given experiment. Peak and area measurements are relatively easy to compute and have direct intuitive appeal, but they prove difficult to use when the data bases are large, the ERPs complex, and the experimental design multifactored. Multivariate techniques provide a useful solution in such cases.

The ERP data analyst's task typically consists of three steps. First, ERP components are identified. In this context, we have discussed the value of principal component analysis combined with visual inspection. Second, the magnitude of components is measured. Computations of ERP peak and area measures, PCA component scores, and discriminant scores are all valuable approaches. Finally, differences between ERPs are assessed. This step usually involves a repeated-measures analysis of variance for peak, area, or principal component scores. Differences are directly assessed in discriminant analysis. As was noted, analysis depends upon the determination of a reasonable baseline.

We wish to emphasize that our intent was not to provide a cookbook for data analysis; any such cookbook would be worthless. There is an unfortunate tendency, derived from the strong influence of hypothesis testing, to seek procedures that, through some manipulation of the data, arrive ultimately at a magic number known as the level of significance. We prefer to view data analysis as a heuristic that provides the user with a set of tools that allow rich and interactive manipulation of data. The same data can be viewed from many vantage points. The waveforms need to be examined and measured in many different ways until a coherent and intellectually satisfying picture emerges. In this endeavor, multivariate techniques, at least in our experience, have proven a valuable aid.

BEFORE AVERAGING: PREPROCESSING SLOW POTENTIAL DATA WITH A WIENER FILTER[1]

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Two models for the generation of event-related potentials (ERP) may be distinguished: (1) an event-locked model, and (2) a latency-variable model. The event-locked model assumes that each stimulus event initiates slow potentials after a certain latency, that this latency remains constant from one trial to another, and that, within each ERP, rank-orders of amplitudes and latencies for negative and positive peaks remain unchanged. The latency-variable model assumes that the initial latency for an ERP varies from one trial to another, but that amplitude and relative latencies for these waves, within each ERP, remain unaltered from one trial to another.

If ERPs were generated according to the latency-variable model, averaging over trials would be improper for estimating a true waveform because averaging techniques require a fixed latency for generation of ERPs. A variety of methods have been used to capture ERPs under the latency-variable model (e.g., Childers and Pao 1972, Pfustscheller and Cooper 1975, Weinberg and Cooper 1972, Woody 1967, Sayers et al. 1974). The results seem to confirm the validity of the latency-variable model by showing considerable variability in the initiation time of ERPs from one trial to another.

Most researchers, however, prefer the averaging method (thus adopting, willingly or unwillingly, the event-locked model) because it offers conceptual as well as computational simplicity. A persistent problem in averaging, however, is that a large number of trials must be averaged to obtain true ERP waveforms that are relatively free from the noise of spontaneous electroencephalographic (EEG) activity. A linear, non-time-varying filter derived from the theorem of Wiener and Khintchin (Wiener 1964, Walter 1969) has been said to provide a significant improvement in the averaging method when this "Wiener filter" is used to preprocess individual records before averaging.

The purpose of this paper is to describe and evaluate the Wiener filter as applied to single-trial data. The filter was first used on an averaged evoked potential (EP) based on artificially generated "toy" data (Walter 1969). Later, Nogawa et al. (1973a, 1973b, 1973c) published a FORTRAN algorithm for the filter and applied it to visual (V) EPs from human subjects. They noted that Wiener filters caused a significant loss of fast frequency components in VEPs. This appreciable loss of faster frequency components in Wiener-filtered VEPs created some concern among researchers. Some felt that the filter was too "heavy" because it reduced, in additon to noise, some peaks in VEPs that were often of interest. To overcome these problems, a modification of the filter was suggested by Doyle (1975) and by Walter (1975), as well as Nogawa (personal communications). A recent paper by Ungan and Basar (1976) showed, however, that loss of faster frequency components in Wiener-filtered EPs remains a problem.

Despite some persistent problems with the Wiener filter, it could still be very useful in signal processing (see, for example, Rosen et al. 1975), because it has some desirable attributes. First, the filter could be applied to remove noise from single records without introducing phase shifts. Second, effectiveness of the filter to enhance signal/noise ratios could be elevated by comparing the filtered single record with a corresponding raw record.

Description of the Wiener filter

The Wiener filter is a digital filter in which the gain or filter weight for each frequency band varies from 1 to 0, depending on signal/noise ratio. If a frequency band contained only "response" or "signal," the filter weight would be 1, passing all of the activities in that frequency band; the filter weight of 0 would be assigned to frequency bands that contained nothing but "noise." In the Wiener filter analysis, the response or signal would be those frequency components phase-locked to the time of the stimulus event over all of the available trials for averaging.

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Although the Wiener filter for the latency-variable model could be written (Walter, personal communication), the filter as discussed in this paper is able to handle only those cases where response is assumed to have non-time-varying waveform from one trial to another with a response that starts with a fixed latency from the time of stimulus event (event-locked model). First, the ERP is written as:

$$X_i(t) = r_i(t) + n_i(t) \qquad (1)$$

where $X_i(t)$ is the observed voltage at time t of the ith trial, $r_i(t)$ is the "response" voltage at time t of the ith trial, and $n_i(t)$ is the "noise" at time t in the ith trial. This model states that an observed voltage in the EEG record after a stimulus event is composed of response and noise.

For each trial, the measurement of voltage of the EEG record is repeated many times at regular intervals to produce a time series of $X_i(t)$. For instance, examples in this paper used EEG records that had 256 data points measured every 15.625 msec (a sampling rate of 64 samples/sec).

The second step in Wiener filtering is to do a discrete Fourier analysis (or a harmonic analysis) of $X_i(t)$. Mathematical details of the analysis can be found in discussions of time series analysis (e.g., Anderson 1971, Bloomfield 1976, Jenkins and Watts 1969, Walter 1969). In this study, the analysis was performed up to the highest frequency admissible with the sampling rate (Nyquist frequency) using the Fast Fourier Transform (FFT) algorithm of Nogawa et al. (1973c). The analysis yielded sine and cosine Fourier coefficients for each frequency, totaling 129 cosine coefficients and 127 sine coefficients for the 256-data-point record. These coefficients were kept in computer core. Storage of these coefficients as well as the average overall EEG records meant that phase information related to stimulus onset was retained for each frequency component. Eight EEG records were evaluated; thus, after FFT, there were 256 x 8 = 2048 Fourier coefficients in computer core. Computation of these coefficients was followed by calculating spectral estimates centering at 0.25, 0.50, 0.75, and so on, to 32 c/sec (Nyquist frequency). The data yielded 128 "line" spectral estimates per EEG record.

The third step is to compute an average spectra, $\overline{S}(X)$ [SP(N) in Nogawa's notation]. There were eight spectra, one spectrum for each EEG record (trial), each spectrum ranging from 0.25 to 32 c/sec. To obtain $\overline{S}(X)$, the eight spectra were averaged at each frequency over the 128 line spectrum estimates.

The fourth step is to compute a spectrum of averaged EEG records or averaged ERPs, $S(\overline{X})$, or PAVA in Nogawa's notation.

In terms of the model represented by equation (1), the mathematical manipulations for averaging spectra can be expressed as:

$$\overline{S}(X) \simeq S(r) + \overline{S}(n) \qquad (2)$$

where $S(r)$ is the spectral intensity of the response, and $\overline{S}(n)$ is the averaged spectral intensity of the noise. It should be observed that $\overline{S}(X)$ is not exactly equal to the sum of $S(r)$ and $\overline{S}(n)$ because $\overline{S}(X)$ under this model has a third term that approaches zero only when a sufficient number of trials are averaged.

The spectrum of the averaged ERPs is quite different from $\overline{S}(X)$ because the process of averaging N number of EEG records reduces the variance of noise in these records by 1/N (see Regan 1972, Walter 1975). Thus, for the model the spectrum of the averaged ERPs is:

$$S(\overline{X}) \simeq S(r) + \frac{1}{N}\overline{S}(n)$$

Equations 2 and 3 provide an estimate of two unknowns. S(r) and S(n), the spectra of response and noise. Further algebraic manipulations are required to solve this simultaneous equation for S(r):

$$S(r) = \frac{(N \times S(\overline{X})) - \overline{S}(X)}{(N-1)} \qquad (4)$$

and for S (n):

$$S(n) = \overline{S}(X) - S(r) \qquad (5)$$

Then, a ratio of the estimated signal-to-noise spectra may be computed for the time series X as follows:

$$H = \frac{S(r)}{S(r) + S(n)} = \frac{S(r)}{\overline{S}(X)} \qquad (6)$$

where H is the gain factor for the Wiener filter of the individual EEG record or trial. In the examples used, we computed a ratio for each line spectrum. This H would be 1 if the record contained nothing but response, or 0 if S (r) were 0.

The H may now be used to "correct" Fourier coefficients, C. Thus, a new set of Fourier coefficients, Y, would be defined as:

$$Y = H \times C \tag{7}$$

For instance, cosine and sine coefficients at 2.5 c/sec were 2.625 and 0.833 before correction, and H for this frequency band was estimated to be 0.718. Then Y would be 1.885 (= 2.625 x 0.718) for the corrected cosine value and 0.598 for the corrected sine coefficient.

The fifth step is to regenerate the Wiener-filtered single EEG record (or trial) using these corrected Fourier coefficients. This is done by obtaining the Fourier inverse (again, details are available in the previously cited references). The Fourier inverse can be performed so that either the response or the noise can be regenerated in the time domain.

Doyle (1975) has described the difference between Wiener filtering of individual EEG records, (see equation 6) and the averaged ERP. For averaged (A) ERPs:

$$H(\text{Ave}) = \frac{S(r)}{S(r) + \frac{1}{N}\,S(n)} \tag{8}$$

Application of Wiener filter to ERP data

In the present study, the Wiener filter was applied to vertex EEG record (referenced to linked mastoids) supplied by H. Weinberg. The EEG was recorded with a time constant of 5 sec and with high-frequency amplifier cutoff set at 30 Hz. Experimental conditions are described by Curry et al. (this volume). We utilized data from one subject under conditions of "standard" and "word-speak."

One set of H was computed for the standard condition, and another set for the word-speak condition. In cases where $N \times \overline{S}(X)$ (where N was the number of EEG records) was smaller than $\overline{S}(X)$ and hence (S(r) became negative (see numerator of Equation 4), we arbitrarily set the corresponsing H for that frequency to be zero.

Fig. 1 shows the result of Wiener filtering individual EEG records obtained under the word-speak condition. Fig. 2 shows the results of analyzing the calibration and word-speak conditions.

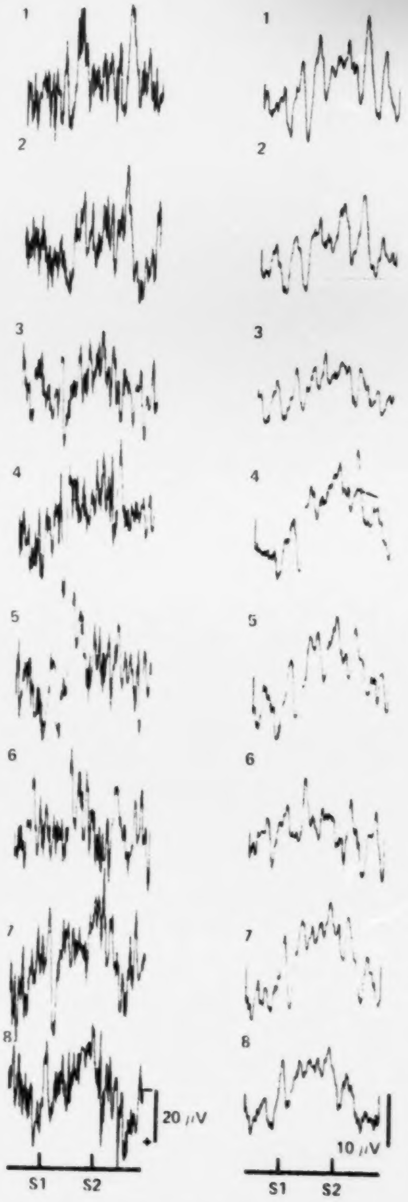

Fig. 1. Wiener-filtered individual records in comparison with raw EEG records for the word-speak condition. The left column shows eight individual EEG records before filtering. The right column shows the same EEG records after Wiener filtering. Wiener filtering seems to have removed most high-frequency noise, still retaining, however, some features of evoked poteneials to S1. Wiener filtering appears to aid in judging strength of dc response in each EEG record; records 3 and 6 exhibited much smaller dc shift response than other single EEG response records. Note that EEG amplitudes for the Wiener-filtered records are amplified twice more than the raw EEG records (see calibration markers.)

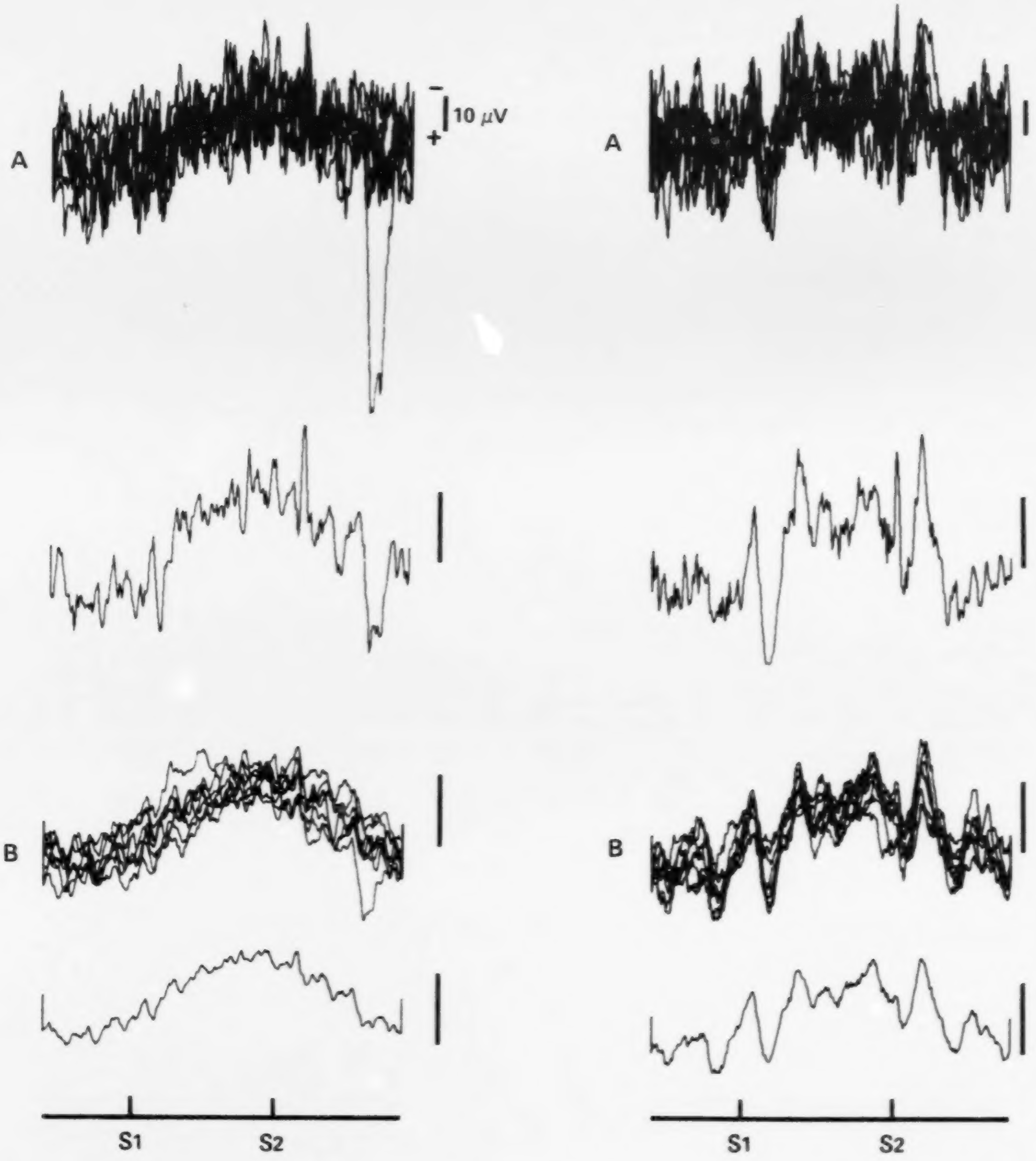

Fig. 2. Analysis of the calibration condition (left column) and of the word-speak condition (right column). Graph A of the left column was obtained by superimposing all eight EEG records, and the average was plotted immediately below. Graph B was a superimposition of eight Wiener-filtered EEG records, and below it is the average of these eight Wiener-filtered EEG records. Comparisons of the two averaged responses show that Wiener filtering tended to attenuate the evoked potential to S1 and also resolution associated with S2. Graph A of the right column was a result of superimposing all eight EEG records under the condition of word-speak, and its average is shown just below. Graph B of the right column is a superimposition of individually Wiener-filtered EEG records (see Fig. 1), and their average is shown just below. In this case, Wiener filtering did not result in loss of the evoked potential component to S1, indicating that this evoked potential component occurred consistently in almost all EEG records. Note that raw EEGs were plotted with one-half the amplification used for all other plots (see calibration marks).

Table 1. Effect of Smoothing over Frequencies on Wiener Filter Gain H

	Calibration condition				Word-speak condition			
c/sec	S(r)[a,b]	S(n)[b]	S(Total)[b]	H	S(r)[a,b]	S(n)[b]	S(Total)[b]	H
0.25	3142	1764	4906	0.640	1996	937	2933	0.681
1.00	-	-	2738	0.000*	528	2269	2797	0.189
2.00	124	986	1110	0.112	763	623	1386	0.551
3.00	203	821	1024	0.198	145	869	1014	0.143
4.00	27	518	545	0.050	178	533	711	0.250
5.00	19	670	689	0.027	17	626	643	0.026
6.00	53	440	493	0.107	-	-	474	0.000*
7.00	26	263	289	0.089	17	241	258	0.064
8.00	5	247	252	0.017	28	123	151	0.183
9.00	-	-	225	0.000*	17	106	123	0.136
10.00	15	200	215	0.068	9	106	115	0.080
11.00	9	83	92	0.098	12	75	87	0.139
Sum	3623	5992	12578		3710	6508	10692	
%	28.8	47.6	100.0		34.7	60.9	100.0	
% Loss	23.6				4.4			

[a] Dash indicates negative value of S(r); for such cases, H was set to be zero and marked by *.

[b] Spectrum intensities S(r), S(n), and S(total) were expressed in terms of squared microvolts.

A check of the calibration (in microvolts) along the Wiener filtered EEG records in Fig. 1 revealed that the filtering resulted in an overall reduction of EEG amplitude, especially of high-frequency EEG. An examination of computer printouts of two sets of H revealed many cases of negative S (r) due to the fact that N x S(X) was smaller than S(X) especially in spectral activities faster than 10 Hz. Walter (1975) and Nogawa (personal communication) suggested that awkward cases of negative S (r) might be avoided by (1) using a larger number of EEG records (hence stabilizing the value of N x S(X) in Equation 4), and (2) smoothing across frequencies to make the variability of the spectral estimate smaller and more stable. The results are listed in Table 1.

Except at 0.25 c/sec, we smoothed five line spectra to estimate the spectrum of response and noise factors. Smoothing over frequencies produced more satisfactory H values than those used in preparing Fig. 1 and 2. Table 1 suggested also that 30% of spectral activities in the average of spectra could represent the response under the calibration condition, and 35 percent under the word-speak condition.

Discussion

Careful examination of H indicated that we would require at least ten EEG records for satisfactory Wiener filtering. This means that Wiener filtering would not substantially improve the chance of obtaining valid averaged ERP under experimental circumstances where a large number of EEG records (trials) could not be obtained. This would suggest that averaging methods are about as efficient as the Wiener filter, and the slight improvement due to Wiener filtering may not justify the computational cost and complexity (Ungan and Basar 1976).

However, there appear to be occasions when use of the Wiener filter might nevertheless be desirable. One such occasion would be when the ERP is superimposed on quite strong spontaneous EEG activity, such as alpha. Nogawa et al. (1973b, 1973c) showed that spontaneous background EEG signals could be effectively removed from averaged ERPs with a Wiener filter. Wiener filters could, therefore, be applied to remove some distortions of averaged ERP that are due to differences in background EEGs seen in different sleep stages.

Another important application of the Wiener filter could be to separate response from noise. For instance, a comparison of the noise spectrum during a prestimulus baseline with that during stimulation would indicate if the stimulus event altered the noise, i.e., the spontaneous EEG.

Furthermore, the Wiener filter might also be useful when spontaneous EEGs of one cerebral hemisphere differ considerably from those of the other hemisphere. The Wiener filter could substantially reduce the risk of observing erroneously an altered ERP of one cerebral hemisphere because of contamination by unusual background EEG.

It should be mentioned here that the Wiener filter should not be regarded as an esoteric mathematical method of analysis. Use of spectrum analysis for removing noise in ERP records (e.g., 60-Hz noise) is a very familiar technique. A DEC PDP 12 computer program set of ANECDOTE, a DECUS program prepared by Cooper et al. (1973), has a well-known data manipulation program that includes Fourier analysis. In addition, it allows the deletion of certain harmonic components, and resynthesis of remaining harmonic components, allowing a return to the time domain. This process of Fourier transform, followed by manipulations of Fourier coefficients, followed by the Fourier inverse is similar to the Wiener filter technique.

A major difference between the Wiener filter algorithm in this paper and those found elsewhere is the ready accessibility of all Fourier coefficients for further manipulation. Coefficients are stored in computer core. Thus, we can combine other spectrum analysis approaches with Wiener filtering. For example, Sayers et al. (1974) computed the harmonic of an auditory (A) EP to a strong stimulus, retaining the phases of these harmonics. They then obtained another AEP, but in response to a much weaker stimulus, resulting in a poorly defined AEP. They did the harmonic analysis on this poorly defined AEP, but replaced phases of the harmonics by those obtained from the AEP to the strong stimulus, the well-defined AEP, and then computed the Fourier inverse. They noted that this "phase-forcing" resulted in an appreciable improvement in determining the AEP to weak stimulation. An obvious extension of this technique would be to employ this phase-forcing on the Wiener filtering of individual EEG records to compensate for latency jitter from one record to another.

As clearly indicated by Ungan and Basar (1976), one unresolved problem of the Wiener filter is related to the length of the time series included in the analysis. Is 0.2 sec duration after the stimulus event needed for Wiener filtering, or 0.5 sec, or even 4 sec? This question appeared to be resolved by the trial and error method. In fact, it appears that critical information about the duration of a signal or response in EEG records can be obtained by carefully examining the size of H and S(r) (Nogawa, personal communication). Suppose a signal persisted for 0.5 sec. H and S(r) would reach maximal value using an analysis epoch of about 0.5 sec, and then diminish as the length of the epoch increased. Thus, it appears possible to estimate signal duration by systematically incrementing the analysis epoch until maximal values of H and S (r) are obtained.

Summary

Wiener filtering was described as it applies to nonaveraged EEG signals. A FORTRAN algorithm developed by Nogawa and his colleagues was modified and applied to a sample set of data. Wiener filtering of individual EEG records resulted in clear response waveforms, but such improvements were accompanied by significant loss in faster frequency components when compared to the averaged ERP. The loss in faster frequency components resulted in the loss of some significant peaks in the averaged ERP, which were easily seen with the usual unfiltered averaging technique.

It was suggested that the Wiener filter should not be used as a method of replacing the usual averaging techniques, but rather as a preprocessing method that has some supplementary advantage to averaging. Application of the Wiener filter combined with other spectral analysis methods was also discussed as an additional method for increasing usefulness of the Wiener filter.

Acknowledgment

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SIMPLE DIGITAL FILTERS FOR EXAMINING CNV AND P300 ON A SINGLE-TRIAL BASIS

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Evoked potentials can usually be characterized as consisting of the sum of a response, synchronized with the stimulating event that elicits it, plus on-going, spontaneous neuroelectric activity that is not related to the stimulus event. For data processing purposes, event-related activity is referred to as "signal," and spontaneous activity as "noise." The noise is often of sufficient intensity to obscure the signal. Computation of an average response over several trials is usually used to attenuate noise interference.

Average response computation has long been known to be a valid procedure when the signal is invariant from trial to trial. If the signal is not invariant, then averaging across trials can result in an imprecise or misleading average waveform. Procedures have been devised to deal with such a situation (Burns and Melzack 1966; Woody 1967; Ruchkin 1968, 1971; Ruchkin and Sutton, in press; Glaser and Ruchkin 1976). A useful first step in dealing with trial-to-trial variation of the signal is to inspect the data on a single-trial basis. Such inspection can provide insights that lead to a fuller understanding of the nature of the data and help in devising further, more refined data processing procedures.

In order to profitably examine single-trial data, some attenuation of the noise is desirable. This can be achieved by operating upon each evoked potential with a suitable linear filter, provided (1) the power spectra of the signal and noise differ sufficiently, and (2) the signal amplitude is sufficiently large with respect to the noise.

These two conditions can occur for slow event-related potentials such as the contingent negative variation (CNV) and P300 components recorded from the scalp of man. Much of the power in CNV and P300 waves is concentrated at frequencies below 10 Hz, while the spectrum of the background electroencephalogram extends to frequencies well above 10 Hz. If the potential's amplitude averaged over the 500 msec preceding the start of a trial is used as a baseline, the root mean square (rms) level of the noise usually ranges from 9 to 13 μV, while the CNV peak amplitude ranges from 5 to 15 μV and the P300 peak amplitude ranges from 15 to 25 μV. Such data can be effectively low-pass filtered so that examination of the CNV and P300 components in single-trial records is feasible.

Methods

Off-line filtering of the digitized data was implemented on a general purpose digital computer. The data were previously stored on magnetic tape. The sampling rate was 62.5 samples/sec.

The basic filtering algorithm consists of averaging together the amplitudes from 2L + 1 adjacent time points. The smoothed or filtered output at time point mT is defined by

$$x(mT) = \frac{1}{2L+1} \sum_{k=-L}^{L} r[(m+k)T] \qquad (1)$$

The interval between time samples is denoted by T. r(mT) denotes the amplitude of the recorded evoked potential at the m^{th} time point. x(mT) denotes the amplitude of the filtered version of the evoked potential. L specifies the number of adjacent time points used. Thus, x(mT) is computed by averaging together the evoked potential amplitudes at time point mT plus the amplitudes at the L time points preceding point mT and the L time points following mT. The computation is temporally symmetric: x(mT) is obtained from an equal number of equally weighted time points preceding and following mT. An important consequence of this temporal symmetry is that the resulting filter causes no phase shift. The filtered data are therefore free of phase distortion.

The transfer function, W(f), which expresses the filter's gain as a function of frequency, is given in Equation 2 and is plotted with the solid curve in Fig. 1 (Oppenheim and Schafer 1975, Glaser and Ruchkin 1977).

$$W(F) = \frac{\sin(2L+1)\pi TF}{(2L+1)\sin \pi TF} \qquad (2)$$

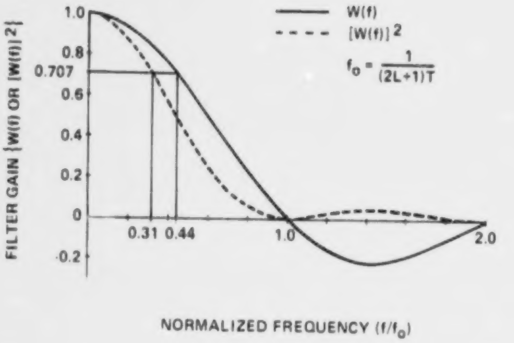

Fig. 1. Plot of filter gain as a function of normalized frequency for the one-step filter (solid line) and the two-step filter (dashed line).

The frequency $f_0=1/[(2L+1)T]$ is the first (lowest) frequency at which W(f) passes through zero. f_0 is a useful parameter for characterizing the filter. It relates filter bandwidth to both the sampling interval and the number of time points used for smoothing or averaging. Filter gain, W(f), is plotted versus normalized frequency, f/f_0, in Fig. 1. The figure indicates that the averaging algorithm produces low-pass filtering. We use the half-power frequency, at which point the filter gain is 0.707 (or, equivalently, -3 dB), to indicate the upper cutoff frequency of the filter. Thus, the filter's pass-band is from 0 to $0.44f_0$.

We refer to Equation 1 as a "one-step" filter. It is readily implemented on a digital computer. Its performance may be adequate in many situations. However, inspection of Fig. 1 indicates that it has a troublesome property. The transfer function has a relatively high secondary peak in the frequency range between $1.2f_0$ and $1.6f_0$. This means that strong noise components in that range may not be effectively attenuated.

A way of dealing with this problem is to reapply the same averaging procedure specified by Equation 1 to the x(mT) waveform, the resultant of the original filtering operation. It can be shown that the transfer function corresponding to this "two-step" filter algorithm is $[W(f)]^2$ (Oppenheim and Schafer 1975, Glaser and Ruchkin 1976). The dashed curve in Fig. 1 is a plot of $[W(f)]^2$ versus f/f_0. The pass-band for this filter extends from 0 to $0.31f_0$ and the secondary peak magnitude in the 1.2 to $1.6f_0$ frequency range is much smaller than for the one-step filter (by a factor of approximately 0.212). It should be noted that the two-step filter is also temporally symmetric and so it too has zero phase shift. A total of 4L+1 time points from r(mT) are utilized in order to compute the amplitude at each time point of the two-step filter output, 2L points preceding and 2L points following time mT.

Results

An example of the use of one-step filters is provided in Fig. 2. The data are from a paradigm in which the second of a pair of flashes elicited a P300 potential (Ruchkin and Sutton 1973 and in press). The interflash interval was 880 msec. The effective pass-band of the recording system was from 0.1 to 30 Hz. The data were digitized over an epoch starting 500 msec prior to the first flash and extending for 2500 msec after the first flash.

Evoked potential records for three selected single trials and the average obtained from these and 81 other trials are plotted in each of the four columns. The top row is a plot of the data when no filtering was used. The second, third, and fourth rows are plots of the data after one-step low-pass filtering with half-power frequencies of 5.5, 3.1, and 1.6 Hz, respectively. The filters were implemented as follows. Since the sampling interval was 16 msec, $f_0 = 62.5/(2L+1)$ Hz and the half-power (-3 dB) frequency is $0.44f_0 = 27.5/(2L+1)$ Hz. Thus the 5.5-Hz low-pass filter utilizes 5 time points (L=2), the 3.1-Hz filter utilizes 9 time points (L=4), and the 1.6-Hz filter utilizes 17 time points (L=8).

Inspection of the average response waveforms in the fourth column suggests that much slow potential detail is preserved when the 0- to 5.5-Hz low-pass filter is used. Use of narrower band low-pass filters, such as a 1.6-Hz filter, results in considerable waveshape distortion. In our experience, a 5.5-Hz low-pass filter is generally suitable for simple inspection of single-trial P300 and CNV data.

While one-step filtering is often satisfactory, a two-step filter with the same half-power frequency will attenuate high frequency noise more effectively. This can be inferred from Fig. 1. Note, however, that a two-step filter requires about 50% more computer execution time than a one-step filter with the same half-power frequency.

We have found two-step filtering is sometimes necessary when estimating P300 peak latencies in single-trial records. We found that when a peak detection procedure is utilized, preliminary filtering of the data with a 3.1-Hz low-pass filter generally yields most satisfactory results (Ruchkin and Sutton, in press). For subjects exhibiting low level alpha activity, a one-step filter with L=4 is adequate. However, due to the secondary peak in the transfer function, high intensity alpha in the 9- to 11-Hz band is not sufficiently attenuated. For subjects with such alpha activity, use of a two-step filter with L=3 and a

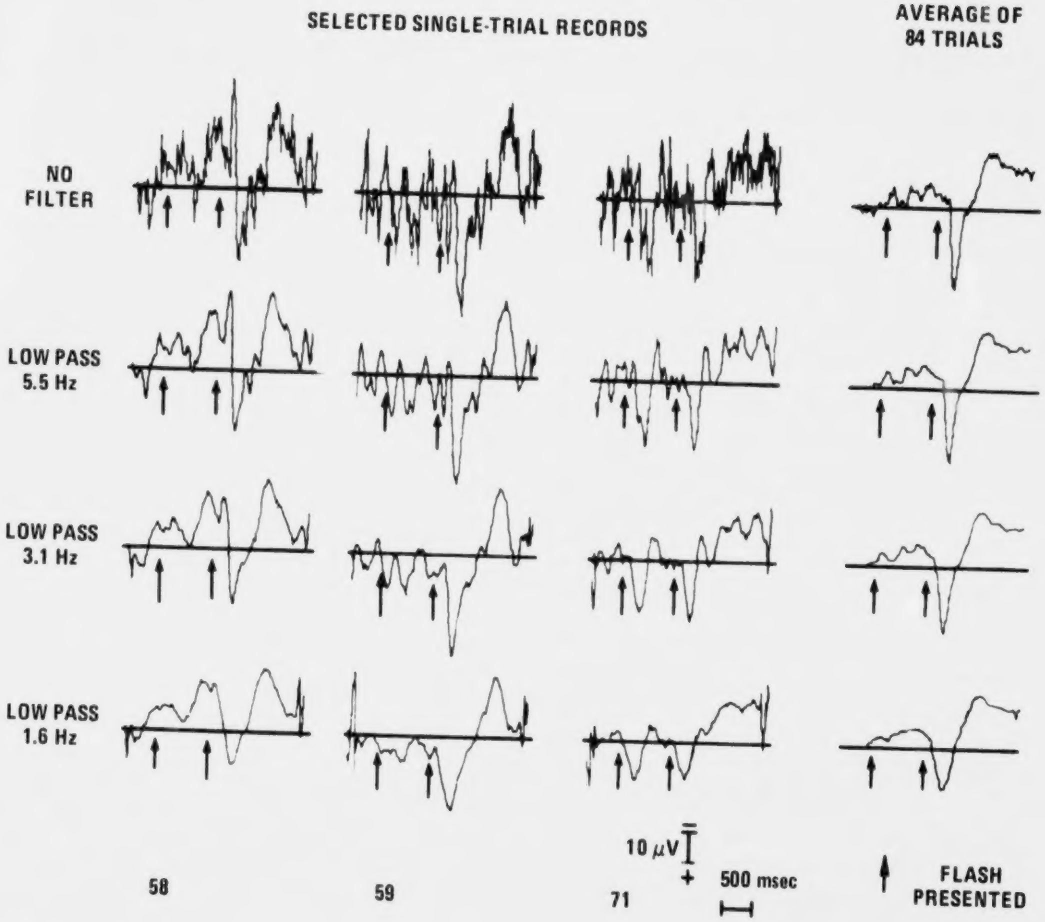

Fig. 2. Plots of single-trial evoked potential records for three selected trials and the average evoked potential for 84 trials. No filtering was used for the records in the top row. The results of applying single-step low-pass filtering with half-power frequencies of 5.5, 3.1, and 1.6 Hz are illustrated in the second, third, and fourth rows. The time epoch is 3 seconds.

half-power frequency of 2.8 Hz has yielded satisfactory results.

Discussion

The rationale for using the low-pass filters described above is largely pragmatic and empirical. The filters are readily implemented. Their capability for attenuating noise while passing P300 and CNV activity appears to be satisfactory. They are not "optimal" in the sense of least mean square error filters (Wiener 1949, Walter 1969, Nogawa et al. 1973, Doyle 1975). However, they do not require the detailed knowledge of signal and noise power spectra nor the degree of computing effort that are necessary for implementation of such "optimal" filters.

Summary

Linear filtering procedures that can make examination of CNV and P300 components on a single-trial basis feasible are described. The filtering procedures are readily implemented by general purpose digital computers. Examples of the use of the filters are provided.

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IMPLICIT SPATIAL AVERAGING OF SURFACE MACROPOTENTIALS

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Macropotentials are, by definition, population estimates of spatiotemporally localized events. The representativeness of these population estimates is crucial in the accurate determination of the functions corresponding to these macropotentials. A major concern of many investigators has been the neuroelectric information lost or confounded due to the summation of time-locked signals. This paper concerns some recent work that suggests that single-trial macropotentials recorded from cortical surfaces may constitute a *spatial* average and may therefore be responsible for an even greater loss of theoretically relevant information than that associated with signal averaging in the time domain.

As Klemm (1976) has noted, the hippocampal theta rhythm (rhythmic slow activity, or RSA) is one of the readiness states that occurs in preparation for adaptive movements. Preliminary to the further study of the function of hippocampal steady potentials and RSA in voluntary movement (Vanderwolf et al. 1975), we studied the surface and depth topographies of RSA in the rat (Gerbrandt et al. 1974; Gerbrandt et al. 1975). Half-cycles of RSA were detected electronically and the resultant detection pulses served to synchronize the sweep of an averaging computer to a constant phase of the RSA monitored at a phase reference electrode located over the neocortex; thus, multiple channels of averaged RSA were obtained as shown in Fig. 1. In Fig. 2, the scalp topography of the average RSA amplitudes and phase are shown. At

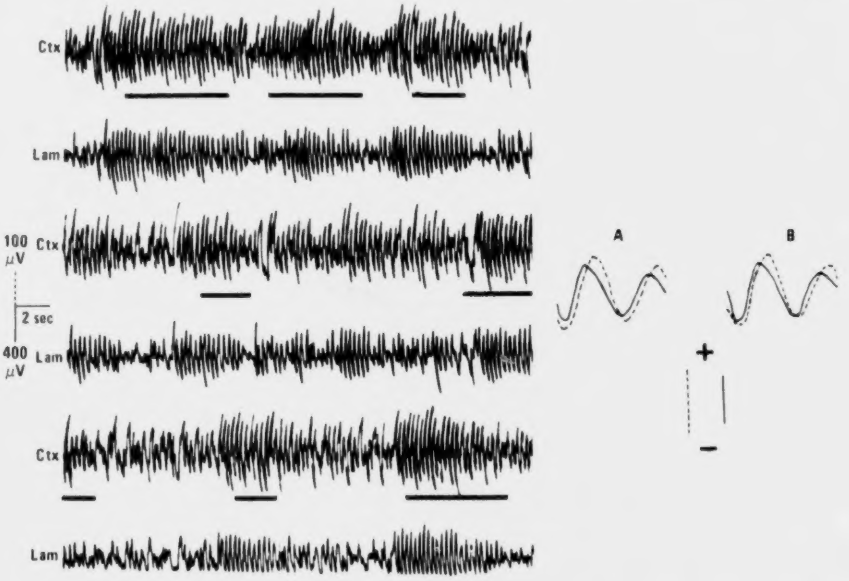

Fig 1. Ctx = neocortical phase reference site indicated by dashed traces in A and B. Lam = laminar electrode, 125 μm above hippocampal pyramidal cell layer, indicated by solid traces in A and B. At right, traces A and B are computerized averages of the raw EEG (50 samples taken during epochs indicated by solid marks under EEG). A was obtained with RSA at neocortical phase reference used as a trigger for zero-crossing "theta" detector, while B used laminar electrode as the trigger. Calibration bars = 100 μ V (solid) and 300 μV (dotted). Phase shift in B=34°, in B = 32°. Trace duration for A, B = 500 msec.

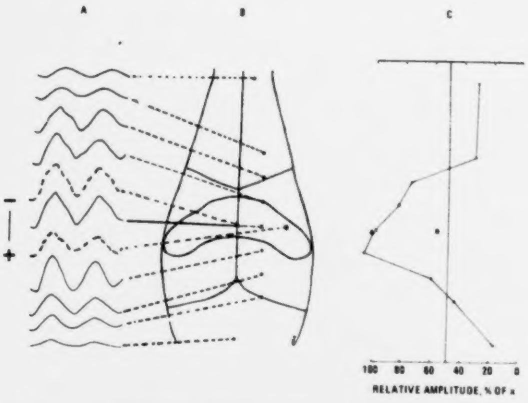

Fig. 2. A indicates RSA averages (50 EEG samples) obtained from active recording sites identified in B (earthed reference). B depicts a rostral view of neocortex with epidural recording sites; underlying hippocampus depicted as horseshoelike structure between bregma and lambda points. The cross-shaped nine-electrode array with 2-mm interelectrode spacings is centered (electrode "x") at 3 mm behind bregma and 2 mm lateral to the midline; candidate indifferent electrodes (triangle and square) are located over the olfactory bulbs and cerebellum. C is a plot of the percent amplitudes of the waveforms in A relative to the waveform recorded at site x. Calibration line (far left) = 200 μV.

the scalp surface, phase shifts of 4° are detected with electrode spacings of 1 mm, and in the same distance, amplitudes do not change more than 25% of the peak amplitude. This poor spatial resolution of latency (phase) and amplitude is not too surprising, considering that neocortically monitored RSA is generated in the dorsal hippocampus rather than in the neocortex (fig. 3); the dorsal hippocampus lies about 2 to 3 mm below the surface of the neocortex. Indeed, a 4° shift is detectable with about a 100-μm movement of an electrode horizontally along the surface of the hippocampus (Winson 1976), although amplitude gradients are no more than two times steeper than those registered along the neocortical surface (Bland et al. 1975).

This tenfold increase in latency on the surface, impressive as it is relative to the adjacent neocortex, is suboptimal compared to the resolution and accuracy of information at right angles to these cortical surfaces. A gradual phase advance of the type shown in Fig. 4 occurs at an average of 4° with as little as 10 μm of laminar electrode movement. In this vertical plane, it is also common to observe a tenfold change in amplitude with an electrode movement of only 400 μm. Finally, a change in the mode of induction of RSA (spontaneously or tactile-induced RSA) does not experimentally alter the amplitude or phase gradients of RSA observed along the surfaces of the neocortex or the hippocampus. Yet, the dentate gyrus of the hippocampus selectively changes in phase as a function of these variables, without concommitant changes in the CA 1 region. If a factor analysis of the phase and amplitude gradients is utilized, even subregions of the single-layered pyramidal cells of the CA 1 region show variances that are independent of the other CA 1 sub-regions. Furthermore, different independent variables selectively control different hippocampal sub-regions (Gerbrandt et al. 1975). The observation that certain independent variables selectively affect only some sub-regions of dendritic branches is understandable, considering the laminated and heterogeneous separation of afferents along the axis of each hippocampal neuron (Fig. 5). However, what is surprising is that we in fact did expect that independent variables that influence such a complex structure could be estimated from the recording of surface macropotentials, or indeed of macropotentials at any single electrode location.

In summary, these findings may have two important suggestions concerning the information lost because of implicit spatial averaging of scalp macropotentials. First, even if it were possible that all of the information "tapped" by an electrode passing vertically along the cortical (hippocampal) cell axis were broadcast upward along the surface plane, the considerable loss of spatial resolution (10 to 100 X)

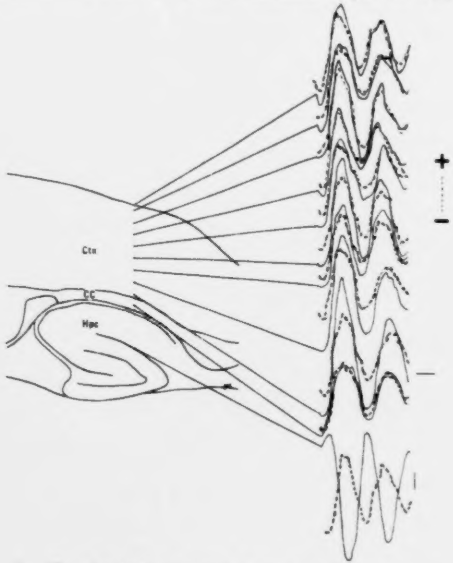

Fig. 3. To the left is a scaled schematic of a parasagittal section at 2.0 mm lateral to the midline. Each point is a scaled 100-μm interval. At right, RSA averages of 20 samples, with the dotted traces representing recordings from the contralateral homotopic phase reference electrode and solid traces taken from the depths indicated at left. Note the in-phase activity recorded to a depth 200-μm above the pyramidal cell layer, with an approximate phase reversal evident at the hippocampal fissure. All calibration bars = 100 μV.

of information, demonstrated here, would result in multiple superimpositions that are likely to cancel some of the real signals. This type of information loss is a spatial analog of the loss due to the temporal smearing, which has been discussed. Unfortunately, few of the variations experimentally induced among the multiple generators of RSA are seen in activities monitored at the cortical surface. Thus, spatial averaging imposes the additional difficulty that only a small subset of the variables that determine each function are likely to be sampled at the cortical surface.

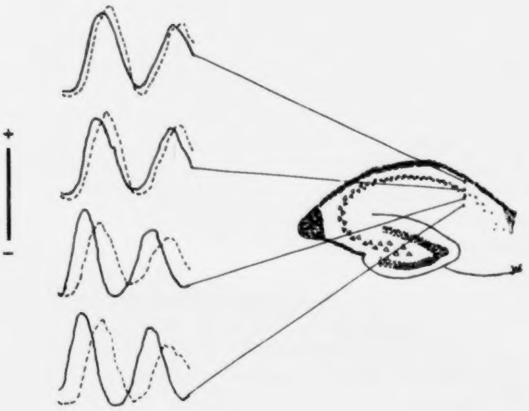

Fig. 4. At the right is a scaled schematic parasagittal section through the hippocampus at 2.0 mm lateral to the midline. To the left, RSA averages are shown (50 trials summated), where dotted traces represent activity recorded from a contralateral homotopic phase reference electrode, and solid traces are RSA waveforms averaged at the indicated depths of the hippocampus. Phase shifts in the hippocampal traces are, beginning at the top, 18°, 38°, 76°, 104°. Calibration bar represents 100μV for phase reference traces and 200 μV for hippocampal traces.

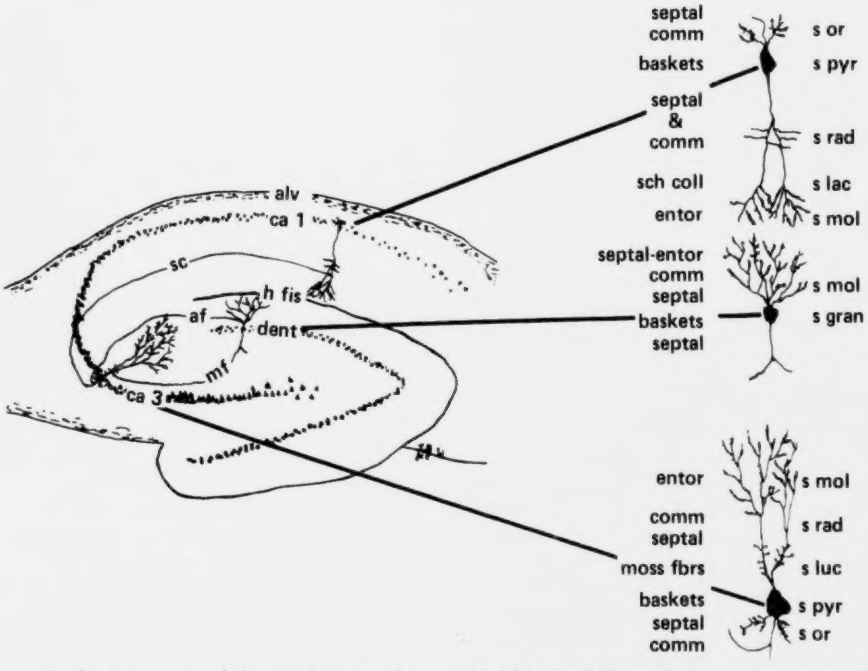

Fig. 5. The interlocking pattern of the single-layered pyramidal (CA1, CA3) and dentate granule cells (dent) and their intrinsic connections (mf=mossy fibers, sc=Shaeffer collaterals), are shown schematically on the left. The sources of the laminated pattern of afferents for each type of hippocampal neuron are shown schematically on the right (septal, commisural, etc.).

NEUROMETRICS: QUANTITATIVE ELECTROPHYSIOLOGICAL ANALYSIS FOR DIAGNOSIS OF LEARNING DISABILITIES AND OTHER BRAIN DYSFUNCTIONS[1]

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At the present time no quantitative criteria exist for the accurate separation of learning disordered children with an organic basis for their impairment from children with primarily functional disturbances or from normal children. The difficulty of this differential diagnosis can be readily ascertained by examining any recent volume on this topic (e.g., Wender 1971, Walzer and Wolf 1973) or by examining current procedures for evaluation and treatment of such children. The importance of proper diagnostic capability for this disorder can be appreciated if one realizes that current estimates of its incidence in the U.S. population range between 5 and 15% (Wender 1971). With early identification and subsequent monitoring of children at risk for cognitive and behavioral problems, intervention could be initiated at the first signs of difficulty.

The diagnostic tools presently available to aid in this endeavor have severe limitations. Classifications are often based upon vague, intuitive observations of behavior of ambiguous origin, or upon psychometric measures of product which fail to make process explicit. There are too many ways to produce an inappropriate behavioral test response. The techniques of classical neurological examination are not optimal for the analysis of subtle dysfunctions in information processing, storage and retrieval. The conventional electroencephalogram (EEG), evaluated by traditional methods of visual inspection, has yielded suggestive but inconsistent findings of abnormal features in children displaying difficulties in learning (e.g., Burks 1960, 1968; Capute et al. 1968; Cohn and Nardini 1958; Ellingson 1954; Grunewald-Zuberbier et al. 1975; Klinkerfuss 1965; Pavy and Metcalfe 1965; Satterfield 1973; Satterfield et al. 1972; Wikler et al. 1970). More recently, studies of the sensory average evoked potential (EP) have suggested that such measures of brain function may reflect aspects of information processing or cognitive functions (see reviews by Regan 1972, John and Thatcher 1977). However, most EP studies of learning disabled children have focused upon gross sensory reactivity rather than indices of information processing and have further suffered from the limitation of qualitative visual evaluation (e.g., Buchsbaum and Wender 1973, Conners 1970, Hall et al. 1976, Halliday et al. 1976, Preston et al. 1974, Prichep et al. 1976, Saletu et al. 1973, Satterfield 1973, Satterfield et al. 1972).

Several conclusions may thus be drawn concerning the present status of the field of assessment of learning disabilities in children: (1) The EEG and EP, assessed under various conditions of information processing, potentially provide a fairly direct insight into brain functions related to sensory, perceptual and cognitive processes likely to be relevant to learning and performance. (2) In order to take optimal advantage of these indices, it is necessary to devise a technology that will derive precise quantitative measures of salient features of the EEG and EP under conditions that "challenge" a wide variety of brain functions devised to reflect such informational processes. (3) neurobehavioral measures should be reduced to numerical representations permitting the use of mathematical and statistical methods of data analysis. (4) Display and evaluation methods are needed to evaluate individual data referred to normative data and to present results in a clinically comprehensible and concise way.

A new technology known as "neurometrics" has been developed to meet these needs. The purpose of

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[2] On leave from the University of Connecticut

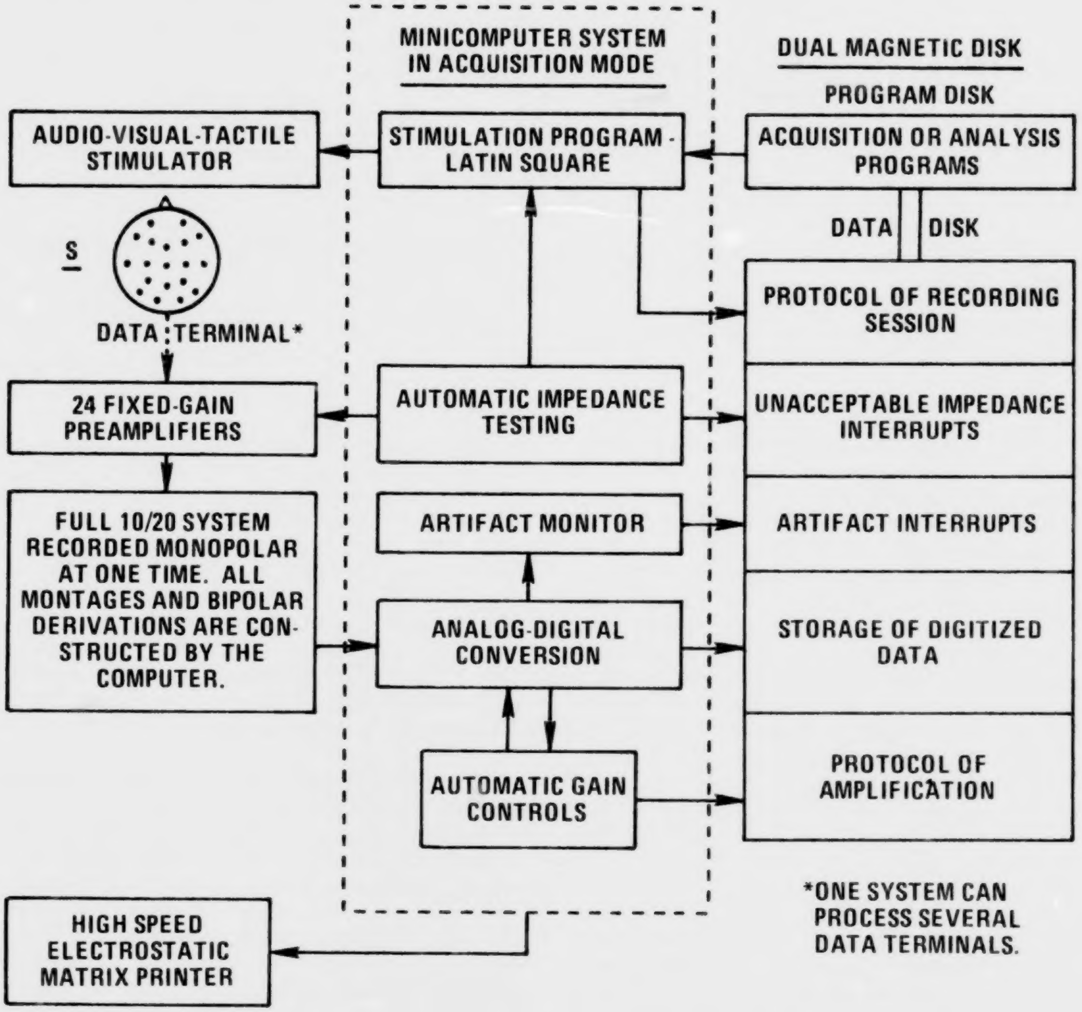
MINICOMPUTER SYSTEM IN ACQUISITION MODE
DUAL MAGNETIC DISK
PROGRAM DISK
AUDIO-VISUAL-TACTILE STIMULATOR
STIMULATION PROGRAM - LATIN SQUARE
ACQUISITION OR ANALYSIS PROGRAMS
DATA
DISK
S
DATA TERMINAL*
PROTOCOL OF RECORDING SESSION
24 FIXED-GAIN PREAMPLIFIERS
AUTOMATIC IMPEDANCE TESTING
UNACCEPTABLE IMPEDANCE INTERRUPTS
FULL 10/20 SYSTEM RECORDED MONOPOLAR AT ONE TIME. ALL MONTAGES AND BIPOLAR DERIVATIONS ARE CONSTRUCTED BY THE COMPUTER.
ARTIFACT MONITOR
ARTIFACT INTERRUPTS
ANALOG-DIGITAL CONVERSION
STORAGE OF DIGITIZED DATA
AUTOMATIC GAIN CONTROLS
PROTOCOL OF AMPLIFICATION
HIGH SPEED ELECTROSTATIC MATRIX PRINTER
*ONE SYSTEM CAN PROCESS SEVERAL DATA TERMINALS.

Fig. 1. Functional diagram of computerized digital electrophysiological data acquisiton and analysis system (DEDAAS).

this paper is to provide a general overview of this technology. More detailed descriptions and results from preliminary applications of neurometrics appear elsewhere (see John 1977; John and Thatcher 1977; John et al. 1977).

Data acquisition procedures

An automatic digital electrophysiological data acquisition and analysis system (DEDAAS) is represented schematically in Fig. 1. Data acquisition is accomplished by a set of 24 EEG amplifiers designed and constructed in these laboratories. These ac amplifiers have a precise fixed gain (10,000 X), a noise level less than 2 μV, a high common mode rejection ratio (106 dB), a frequency response of 0.3 to 70 Hz (6 dB/octave roll off) with a sharp 60-Hz filter to eliminate the need for a shielded room, a high input impedance (10 megohms) to reduce the influence of variation in impedance of scalp electrodes and freedom from drift.

The output of these amplifiers goes to a PDP 11 computer (11/45, 11/10, or 11/03) programmed to automatically calibrate the amplifiers and check electrode impedances. Nineteen amplifiers are occupied by the International Electrode System; channel 20 is used for a pair of transorbital electrodes to monitor eye movement. The remaining channels are available for accelerometer or polygraph recordings as desired.

The full 10/20 system is recorded simultaneously, as monopolar derivations referenced to linked earlobes. Data are transformed on-line into digital format and stored on magnetic tape, obviating the need for off-line analog-to-digital conversion. Conventional bipolar montages or any desired compound electrode are subsequently constructed by computer simulation. We routinely compute data from 57 derivations (i.e., 19 monopolar, 19 coronal bipolar, and 19 saggital bipolar pairs).

Frequency and voltage limits for every channel are continuously monitored by computer to identify data contaminated by eye or body movement, or by high electrode impedance. Questionable data may either be eliminated or marked and stored. To assure the adequacy of artifact rejection, these records are routinely inspected prior to quantitative analysis.

Required stimulus sequences are generated automatically by computer using a stimulator and neurometric battery (NB) described below. Complete stimulation protocols are included in the digital record to permit subsequent automatic data analysis without operator intervention.

The stimulator contains a photo-flash tube, a source of oscillating light, an automatic slide projector, click and pure tone (200, 500, 1000 and 3000 Hz) sources of specified intensity, and a constant-intensity tactile stimulator. A video set and a cassette player provide other stimuli. Appropriate sequences of stimuli define all NB conditions, each condition being a computer subroutine in DEDAAS.

Neurometric test battery

The quantitative electrophysiological test battery, referred to as the neurometric battery or NB, consists of EEG and EP measurements obtained under a variety of standardized conditions. Each condition is designed to probe maturational level and structural integrity of the brain, as well as specific aspects of sensory, perceptual and cognitive functions. The empirical basis of the neurometric battery has been reviewed elsewhere (John 1977). While the NB is based on previous research, the battery will undoubtedly be modified and supplemented as data accumulate and the diagnostic utility of each condition is assessed.

Each condition is considered a test item and yields several scores, which quantify separate features of electrical activity (see below). Differences between responses on different NB conditions constitute an additional source of information about brain function. These composite conditions, in which information obtained under one condition is evaluated relative to that obtained under another condition, are referred to as "challenges." The NB includes a total of 92 conditions and challenges, which are fully described elsewhere (John and Thatcher 1977). Administration of the entire NB requires approximately 50 min of data acquisition. Actual running time may be longer because of "time-outs" caused by artifacts.

Normative data are available for large samples of normal children (age 7-11) and LD children (age 7-18) for the full set of 92 conditions and challenges (Ahn, et al. 1975; Harmony et al. 1973a, 1973b; John et al. 1975, 1976a, 1976b; Kaye et al. 1975; Matousek and Petersen 1973; Otero et al. 1975a, 1975b). For other age ranges norms are available for only a small subset of the NB conditions. More extensive norms are being collected for all conditions and challenges. Table 1 lists the set of test items that presently constitute the NB and indicates the utility of each item.

Quantitative indices

These NB conditions and challenges provide a large volume of EEG and AEP data. From data recorded for each electrode derivation under every condition and challenge, a variety of numerical features are extracted.

Under each EEG condition, twelve 5-sec samples of artifact-free EEG are recorded. Numerical features are computed from each sample separately and the mean values and standard deviations of these are then calculated for the full set of samples. Under each AEP condition, the EP of every derivation is computed from 64 EPs. This computation yields the average signal voltage and its variance at each of 100 time points, sampling at 10-msec intervals across a 1-sec analysis epoch. In addition, a number of indices that are intended to reflect critical features of the response process are extracted from these data. These derived features are computed for the whole analysis epoch and for each of four latency intervals corresponding to components or waveshape segments of special interest. Computed EEG and EP indices may be described briefly as follows:

EEG indices

Absolute power (microvolts squared) in seven frequency bands, i.e. low delta (0.5-1.5 Hz) high delta (1.5-3.5 Hz), theta (3.5-7Hz), alpha (7-13 Hz), low beta (13-19 Hz), high beta (19-25 Hz), and wide band (0.5-25 Hz).

Relative power (% of total power) in low delta, high delta, theta, alpha, low beta, and high beta frequency bands.

Age-dependent quotient (ADQ): A metric reflecting maturational development is obtained for major cortical regions by calculating the ratio between the delta and theta energy usually observed in that head

Table 1. Test Items in the Neurometric Battery

Neurometric test item	Intended purpose
EEG conditions and challenges	
1. Eyes open, spontaneous EEG	Baseline measures
2. Eyes closed, resting EEG	Yields age-dependent quotient
3. Eyes open minus eyes closed	Effect of removal of visual input
4. Photic driving at 2.5,5,10, and 18 hertz	Yields reactivity in delta, theta, alpha, and beta ranges when compared with baseline measures
AER conditions and challenges	
Sensory acuity	
5. 65 lines per inch, 50 percent transmission	Perceived as a blank flash
6. 27 lines per inch, 50 percent transmission	Seen as checkerboard if visual acuity is approximately 20/20
7. 7 lines per inch, 50 percent transmission	Seen as checkerboard unless visual acuity is worse than 20/200
8. 45 db click	Elicits auditory AER unless hearing loss is sufficiently severe to interfere with language acquisition
Pattern perception	
9. Large square	Each contributes to an estimate of perception of differences in geometric forms but preservation of shape invariance independent of size
10. Small square	
11. Large diamond	
12. Small diamond	
13. "b"	Each contributes to estimates of central discrimination between shapes of letters most commonly reversed
14. "d"	
15. "p"	
16. "q"	
Prediction of temporal order	
17. Random versus regular flash	Change in AER waveshape reflects diminished response to predictable stimuli, indicates recognition of repeated temporal sequence
18. Random versus regular click	
19. Random versus regular tap	
20. Phasic habituation	Reveals rate and amount of suppression of information input about a meaningless monotonous event, reflects attention and short-term memory
21. Dishabituation	Indicates whether suppressed input is nonetheless continuously monitored to permit detection of possible change
22. Rehabituation	By comparison with initial phasic habituation, reveals whether suppression of meaningless input is facilitated by memory of previous experience
Sensory-sensory interactions	
23-25. Passive interactions between visual, auditory, and somatosensory systems	Reveals increase or decrease in response of brain as a result of simultaneous presentation of simple stimuli in different sensory modalities
26. Flash followed by click 250 msec later	Measure of recovery cycle after visual input
27. Click followed by flash 250 msec later	Measure of recovery cycle after auditory input
Figure-ground relations	
28-30. Interaction between meaningful visual input (figure, consisting of scenes on a video screen) and meaningless visual, auditory, or somatosensory input (ground)	Reflects dynamic structuring of figure-ground relationships which require discrimination between relevant visual "signal" and irrelevant "noise," which may be wither ipsomodal (video-visual) or cross-modal (video-auditory or video-somatosensory)
31-33. Interaction between meaningful auditory input (figure, consisting of a tape recording of a musical selection or story) and meaningless visual, auditory, or somatosensory input (ground)	Reflects dynamic structuring of figure-ground relationships requiring discrimination between relevant auditory "signal" and irrelevant "noise," which may be wither ipsimodal (music-auditory) or cross-modal (music-visual or music-somatosensory)
EEG conditions and challenges	
35. Eyes open, spontaneous EEG	Replication of initial measures
36. Eyes closed, resting EEG	
37. Eyes open minus eyes closed	
38. Eyes open, beginning, minus eyes open, end	Estimate of effects due to state, such as anxiety about test or fatigue due to testing, versus characteristic individual features displayed across states
39. Eyes closed, beginning, minus eyes closed, end	

region in a normal person the same age as the patient and the amount of delta and theta energy actually measured in the patient. If the ratio

$$\text{ADQ} = \frac{\text{normal energy in frequency band}}{\text{patient energy in frequency band}}$$

is approximately 1.0, the amount of slow activity in the recording is appropriate for a healthy person of that age. Many brain diseases, as well as maturational lags, are reflected by an excess of slow activity and ADQ values significantly less than 1.0. Progress of an abnormal brain state, such as might ensue from head trauma, space-occupying lesion, cerebrovascular accident, or maturational lag, can be followed quantitatively by comparing values of ADQ obtained sequentially at appropriate time intervals. Effects of medication or other treatment can be similarly measured.

Coherence between homologous pairs of derivations (phase-locked correlation) in low delta, high delta, theta, alpha, low beta, and high beta bands.

Amplitude symmetry between homologous derivations in low delta, high delta, theta, alpha, low beta, and high beta bands.

Overall waveshape symmetry between homologous pairs as assessed by the cross-correlation coefficient for the wide-band EEG signal.

AEP indices

The following indices are extracted from EP waveshape and variance, which constitute the initial level of computation.

Signal strength. Energy represented in the EP in four latency intervals, i.e., 40-99, 100-199, 200-499, and 500-999 msec.

Noise. EP variance in the same four latency intervals.

Signal/noise ratio. Average signal strength across each of the four latency intervals divided by the averaged value of the noise during the corresponding interval.

Mean squared first difference, which is proportional to the product of signal energy and mean squared signal frequency.

Pairwise energy asymmetry. The difference in signal strength between homologous pairs of electrode derivations, computed for each of the four latency intervals.

Pairwise waveshape asymmetry. The difference in waveshape between homologous pairs of electrodes, as represented by the Pearson correlation coefficient, computed for each of the four latency intervals.

Peak amplitude and latency for each component identified in the EP.

Peak amplitude asymmetry both absolute and relative for each component.

Amplitude and latency differences between corresponding peaks in homologous electrode pairs.

Amplitude excursions between the peaks of successive negative and positive components.

t-test for significance of differences between waveshapes recorded simultaneously from bilaterally symmetrical derivations. The significance of differences is tested for all points throughout the analysis epoch.

F-test for significance of differences between waveshapes recorded simultaneously from any combination of derivations.

Data reduction, display, and evaluation

AEP morphology

The digitized EP waveshape can be represented as a signal vector in a 100-dimensional time space, where each dimension corresponds to signal voltage at a particular latency point in the analysis epoch. Factor analytic procedures can then be used to determine the actual dimensionality of this "signal space," either for EPs from many derivations in the same individual or from the same derivation(s) in many individuals. It then becomes possible to construct a more parsimonious description of data consisting of the linear combination of a set of terms each defining the relative contribution (factor loading as % signal energy) of each basic dimension (factor) to the signal vector. These linear equations enable great compression of EP data. Every EP in the signal space can be represented by a small set of factor loadings specifying the relative contribution of the same basic set of factors to each of the EPs.

Extracted features

The full NB yields an extremely large volume of data, making obvious the need for compression, evaluation, and display techniques for comprehension of the mass of data available for any individual or population. Group means and standard deviations for normal individuals in each age range of interest, for each quantitative index are calculated, followed by t-tests.

These, and other measures, can be displayed for individuals or populations in ways that facilitate comprehension. Fig. 2 shows an example of the "POPHIS" display for two graphs from two selected sets of subjects. This program plots cumulative frequency curves of both groups superimposed on the

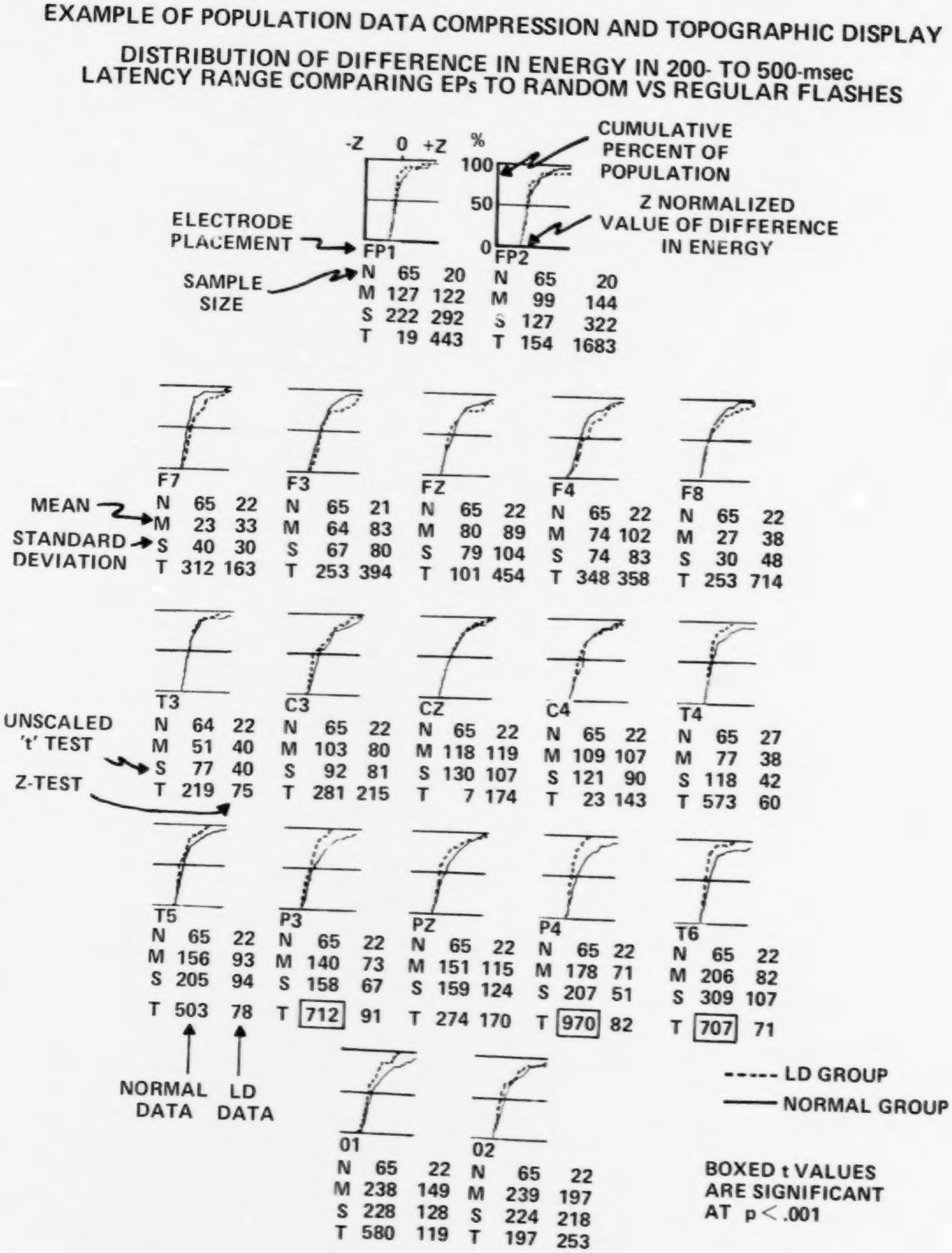

Fig. 2. Compression of data comparing derived features of EP waveshapes elicited by random and regular flashes, recorded from 19 electrode placements of the 10/20 system in a sample of 65 normal and 22 learning disabled children. The overall display represents the topography of the electrode array viewed from above, with the front of the head oriented toward the top of the display. Each graph compares the cumulative distribution of the selected EP features in the two different groups of children (POPHIS program).

same graph, with 19 graphs displayed in the format of a head for each of the three montages (monopolar, saggital, or coronal bipolar). A set of graphs is displayed for each measure, and for each time epoch of the EP. Below each graph in two separate columns are displayed the group N, mean, and standard deviation for the measure for each group, a t-test value, and a Z-test value (both in the row labeled "T"). These programs can be used to display basic measures as well as difference measures comparing bilaterally symmetric locations or differences between conditions that define challenges.

It now becomes possible to implement a strategy considered to be one of the most powerful aspects of the neurometric technique. Each NB index obtained for any individual is subjected to Z-transformation. The individual index is transformed from its original units into a form representing the relative probability of encountering that value for that index among members of a normal reference group. It then becomes possible to define "abnormality" in a statistical sense as a set of improbable values not attributable to random eccentric values due to the large number of items in the measure set.

One useful application of Z-transformed individual NB values is to construct a graphic representation of the anatomical location of improbable indices found across any subset of measures for an individual or group of individuals. In such displays, illustrated in Fig. 3, a localized region on a head diagram represents the anatomical position of each electrode derivation. The density of shading in each local domain is proportional to the degree of departure of represented indices from the normative reference in positive (+) or negative (–) deviations. That is, the more deviant the value, the more dense the entry on the head diagram. Deviations of data within normal limits are indicated by a pair of spots. This representation provides a rapid overview of findings in any individual, providing visual correlation between type and anatomical locus of abnormality. Indices that initially reflect disparate types of dimensions such as voltage, time, latency, or coherence, are now transformed to the common metric of probability. It therefore becomes possible to compare or combine measures that were initially not dimensionally comparable.

The abnormality profile of any individual can now be represented as a Z-vector in an NB-dimensional probability space. The Z-vector for an individual whose NB indices do not deviate significantly from expected values will not be significantly distant from the origin of this space. However, the more deviant an individual's NB indices, the further into the space the corresponding Z-vector will project. The direction in which the Z-vector points corresponds to the diagnostic definition of abnormal electrophysiological activity in the brain of that individual. Thus, abnormality is defined quantitatively by the length of the Z-vector and qualitatively by the orientation of the Z-vector. A distance matrix can now be computed between the Z-vector representing each individual and those representing every other individual in the group being studied, yielding interindividual distances in probabilistic terms. The computation of such a matrix is the starting point for a number of statistical pattern recognition and cluster analysis methods that can be used for the objective classification of groupings of data points in multidimensional spaces. The general field of these classification methods is known as "numerical taxonomy" (Sneath and Sokal 1973).

The prototypic data in Fig. 3 shows five normal and five LD children selected from a larger sample and are to be considered as illustrative examples rather than as invariable findings.

The upper four rows of displays represent the distribution of relative power in the spontaneous EEG, recorded from bipolar derivations with eyes closed. Note the typical excess of slow delta activity, predominantly in posterior head regions of the LD subjects, usually coupled with a deficiency of alpha and sometimes of beta activity. The fifth row shows that the LD subjects show significantly less change in signal energy of the bipolar EP in the latency region between 200 and 500 msec when a flash delivered randomly while the subject is watching a TV cartoon is compared with a flash delivered randomly while the subject looks at the defocussed TV screen. The sixth row shows that LD subjects display significantly less change in signal energy of the monopolar EP in the latency region between 200 and 500 msec when a random flash is compared with a regular flash. The particular head regions displaying this less-than-expected difference when the two conditions are compared vary from subject to subject. Nevertheless, such findings show that LD children tend to display less suppression of P300 to an irrelevant stimulus (ground") in the presence of meaningful environmental input ("figure"). Analogously, they also display less of a tendency to distinguish between predictable and unpredictable events in the environment, reflected in the similarity of late positive EP components elicited by these two different kinds of events.

To date we have collected neurometric data on approximately 1000 learning disabled children and are in the process of submitting this data to cluster analysis. It is our belief that a number of neurophysiologically homogenous subgroups (i.e., groups of individuals with similar electrophysiological profiles of brain function), will be identified within this heterogeneous group of individuals who display common behavioral symptomatology. Further, we expect that many of these subgroups will correspond to diagnostic entities with meaningful functional and etiological

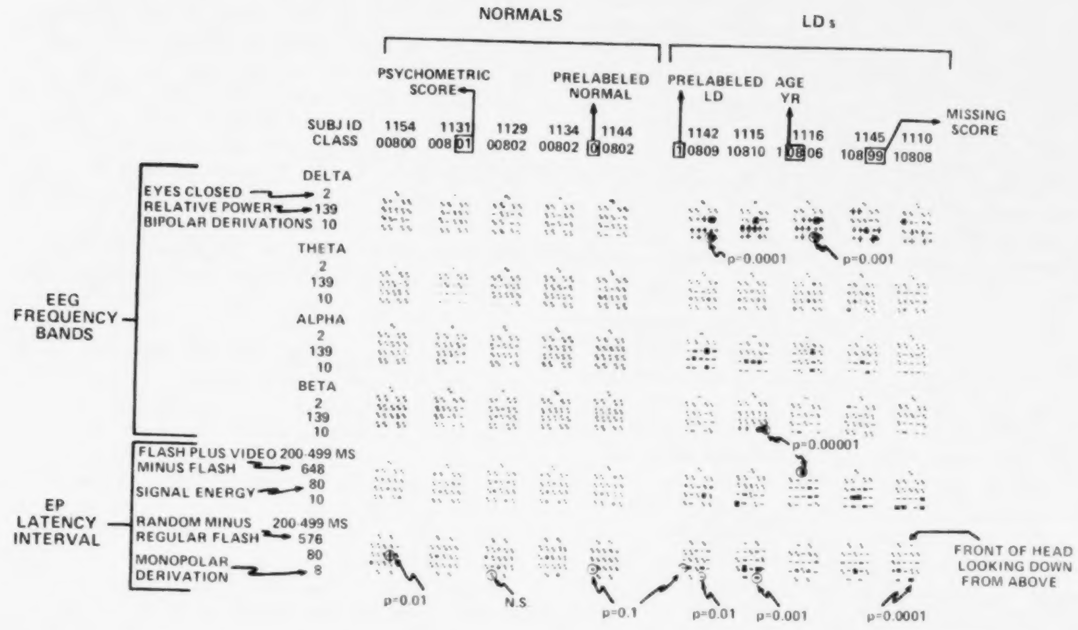

Fig. 3. Illustrative density-coded Z-transformed displays of neurometric indices extracted from various EEG and EP conditions of the NB. Each column of displays represents data obtained from one subject, while each row represents one univariate or multivariate index. Each display represents an array of entries: each entry corresponds to the value of the index measured at that point on the subject's head, while the position of the entries in the array corresponds to the electrode locations of the 10/20 system.

implications. Preliminary results indicate that this will be the case (John 1977, John and Thatcher 1977).

Conclusion

While our primary concern lies with early detection and remediation of subtle brain dysfunctions in learning disabled children, we are also interested in the application of neurometric techniques to other problems that would benefit from more sensitive assesment of brain function (e.g., the problem of senility in the elderly, and neuropathologies such as tumors, strokes and traumatic head injuries). A description of preliminary applications of neurometrics to other groups can be found in John and Thatcher (1977) and John (1977).

Successful application of this new technology should have a number of important consequences. It should extend the domain of electrophysiological assessment into information processing disorders, where present methods are all but useless. It should make possible mass screening for the early identification of victims of such disorders, with increased opportunity for early intervention and remediation. Most important, numerical taxonomy applied to an adequate spectrum of neurometric indices might make possible the differential diagnosis of distinct etiologies within categories of patients now considered homogeneous. Once such differential etiologies are identified, it might be possible to identify their antecedents, institute specific preventive measures, and devise individualized prescriptive remediation effective for their treatment.

COMMENTS ON METHODS OF SIGNAL ANALYSIS AND SIGNAL DETECTION[1]

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It is well known that signal averaging of the EEG is the repetitive summing of event-locked data. The data usually vary in voltage and frequency over a specified interval of time, either preceding or following an event. An implicit assumption underlying use of averaging techniques is that sums of voltages at fixed intervals with respect to the event represent those voltage changes that occur most reliably, i.e., consistently. However, it has always been clear that the sum (or average) of these voltage changes reveals little or nothing about their consistency. Indexes of variability must certainly be considered as a necessary adjunct to any statement of reliability, and many investigators do now include measures of variability as routine qualifications of the average.

The most common meaning of "variability" with respect to event related potentials (ERPs) is the variability of voltages occurring at the same instant in time after or before repetitions of the "same" event. Variability measures are generally used to establish the statistical significance of mean changes in ERPs at specific times after or before different events; different events are usually, but not always, predefined prior to the analysis. However, variability may also be thought of as an independent variable. Under some conditions, evoked potentials (EPs) are more variable. Furthermore, variability may change systematically after or before events. When the event is a stimulus, variability of ERPs may be modified by simple repetition of the stimulus. For example, the variability of voltages within the intervals of N2-P2 of click-evoked potentials seems always to be much less than the variability of N3-P3, although P3 at the end of a contingent negative variation (CNV) may be highly stable. Another frequent observation is this: The variability within a CNV interval may be less near S1 or near S2 than it is elsewhere. I suspect that the variability at S1 and S2 may be a function of the amount and nature of the information contained in these stimuli. Patterns of variability within a CNV or EP interval may be more significant than the mean amplitudes. Fig. 1 shows systematic changes in variability during a CNV interval in which a standard CNV paradigm was used. Fig. 1 also demonstrates that variability of a CNV may also be differentially distributed over the scalp. In this illustration, variability is greater at Fz and Cz than it is at more posterior or temporal derivations.

When considering variability of voltages occurring at the same time after repetition of the same event, it is clear that variability in the amplitude of signals may not be distinguishable from variability in the latency of those signals if only the mean or sum is known. This is a fundamental limitation of averages without concommitant indexes of variability. This limitation is particularly important if the presumed function of averaging is to extract the real signal from noise. This problem leads directly to another issue. Are the characteristics of extracted signals related to the extraction procedures? Put more strongly, the question is: Do extraction procedures in fact *define* the signal? Most people consider extraction procedures to be a method of separating the real signal from noise. This problem is in fact the same encountered by all assessment procedures: Should one set of measures be used to validate another, and if not, what may be used? Electrophysiologists are in a somewhat better position than the inventors of paper and pencil tests for they can apply different procedures to artificial signals of known parameters. The distinction between extraction and analytic procedres rests on the assumption that extraction procedures (like averaging or filtering) do not constitute analysis of the signal. Fundamentally, extraction procedures cannot be distinguished from analytic procedures. Consequently, signal averaging can be thought of as an analytic technique in the same sense that factor analysis is considered analytic.

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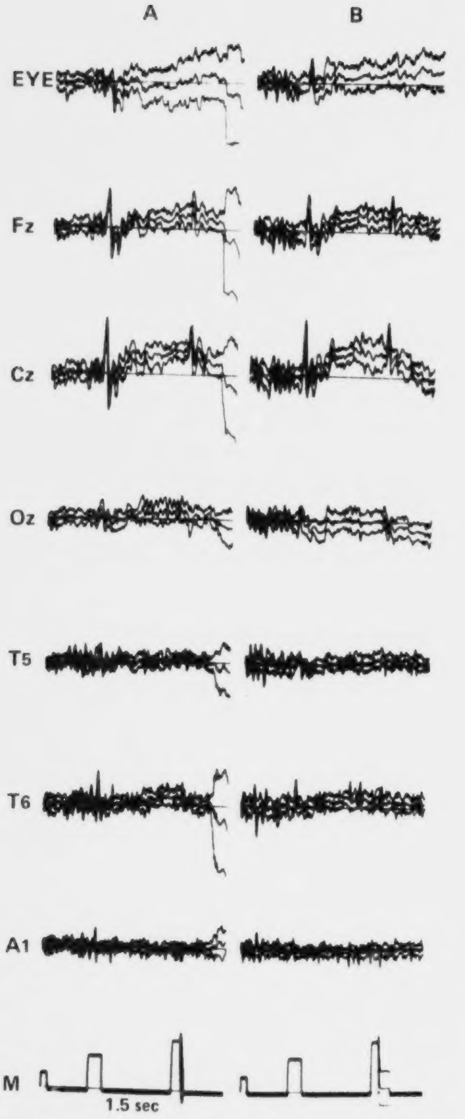

Fig. 1. Changes in the standard deviation of an average CNV during the CNV interval ± standard deviations are plotted above and below each average. A = trials 8–16, B = trials 17–32 of a standard CNV paradigm. M = markers: S1 (tone) occurs at onset of second mark (square wave); S2 (tone) occurs at onset of third mark. Mean reaction time and ± 1 standard deviation of reaction times are shown as offset of third mark. All electrodes were referenced to A2 (A1–A2 record between mastoids). Eye electrode is located on right supraorbital ridge. Note that for all sites, with the exception of A1–A2, variability tends to neck near S1, becoming greater immediately prior to S2. This change in variability during the CNV interval is more characteristic of midline than temporal electrodes.

A frequently used alternative to signal averaging is the simple method of superimposition of single observations or of averages. This is nothing more than an attempt to use the eye as a device for estimating the mean and variability of the superimposed data. When averages are superimposed to display variability of the total set of single trials that enter into the averages, there is an implicit assumption: that the same variability would emerge with an equal number of any random selection of single trials for each average, an assumption that is probably untrue more often than true. On the other hand, superimposition is certainly as reasonably a procedure as signal averaging, and under some conditions may be superior. For example, if the activity concommitant wih the signal, the so-called noise, is discontinuous, superimposition allows detection of those discontinuities, whereas averaging does not.

The statement that signal averaging fails to give specific information about the influence of each trial on the averaged signal implies more than may appear on the surface. One implication is that each individual (single trial) signal may not be an approximation to the real, i.e., significant, signal. There may be no real signal; there is no basis in neurophysiology for believing that there is a unique signal characterizing the effects of successive inputs. There is good reason to believe that each signal is unique and meaningful, that its difference from other signals in the set observed does not simply constitute variability from the presumed real signal. From this perspective, the assumption that the time series recorded actually constitutes noise superimposed on a signal comes into question. Put another way, the use of signal averaging forces us to assume that there is indeed a signal to extract, that the raw data do not constitute in their entirety the signal to be observed. As an example, imagine the following: Following successive presentations of precisely the same stimulus, the ERP was a sine wave changing systematically in frequency as a function of each new stimulus presentation. Averaging these signals would give a new signal that is, in a very real sense, representative of the class of individual sine waves. The variability of each signal could be constructed as variability of the "signal" extracted through averaging. There is a basic question that must be faced: Are we justified in making the assumption that the signal of interest is imbedded in noise? Herning (pre-circulated correspondence) makes this point succinctly by quoting M.A. Brazier who offers the observation that each event in the nervous system, in response to the same stimulus, is different. This salient fact is seldom emphasized. A corollary of this is the argument that the same stimulus is not the same stimulus after all, since it occurs at different times from other instances of its occurrences, and is therefore imposed on a different nervous system. The influence of the stimulus on the nervous system would therefore define the stimulus!

Although limitations on discriminability of the influence of single trials are important, there is perhaps an even more important constraint imposed by signal averaging. Vaughan (1969) proposed the term *event related potential* as a substitute for *evoked potential.* This term was adopted to describe the constellation of potentials that included CNV, P3, N1, N2, readiness potentials, evoked potentials, emitted potentials, slow and infraslow potentials, and others. All shared a common property: they were related to an event, i.e., an input, an output, or a concommitant change in the environment or in the brain. The term *evoked* is inadequate because it does not conceptually describe electrical changes like the readiness potential and emitted potentials. For example, what can be said to evoke a readiness potential? The term *related* in ERP refers to a *temporal* relationship.The focus on temporal relationships was reinforced by the averaging technique, for the technique by its very nature allows to emerge only those signals that have a consistent temporal relationship to a predefined event. Signal averaging implies that the same electrical signal does not occur at different latencies with respect to the predefined event. This is probably the most serious and significant constraint of the technique. It imposes a severe limitation on the evaluation of signals related to information processing, which do not result from immediate stimulus input or precede a response.

Are there alternatives to signal averaging? It is important to again emphasize that extraction and analytic techniques are not conceptually distinct; it is the process of analysis that defines the signal. Thus, what are normally considered analytic techniques could be viable alternatives to signal averaging. Multivariate techniques like factor analysis assume that each event in the nervous system, in response to an input, represents some variability with respect to the real signal. Furthermore, multiple interactions are very difficult to interpret.

Fourier analysis has been used for the analysis of averages and raw data. The interpretation of frequency analysis can be hazardous since Fourier components may result from signal modulation producing artifactual harmonics that are difficult to discriminate from components of the signal. Amplitude modulation presents the same difficulty. However, the major limitation of frequency analysis is related to the major limitation of signal averaging, it gives very little information about when a signal is occurring. This is also true for signal averaging when the signal is not time-locked to an event. It is also true of frequency analysis even when the signal is time-locked to the event. For example, the analysis of a CNV that has this form ▷ would be the same as the one that had this form◁. A partial solution is to successively sample epochs within the record of interest and plot Fourier transforms along a Z axis representing time, i.e., to slide the epoch of analysis along the time domain that contains the signal of interest, in a manner similar to that used by the recognition index (described below). This would allow the determination of precisely when, in addition to which, frequency components within the record were shifting, whether or not data were time-locked to an event. I am now exploring this method as a practical technique. If an index of when the signal should appear is available, frequency analysis of selected epochs could be done for each trial, and the Fourier transforms averaged. Theoretically this would result in no more information than the Fourier transforms of the averaged signal. However, averaging tends to filter high frequencies since they jitter more than low frequencies. Consequently, a frequency analysis of the average would not reflect the presence of high frequencies to the same extent as the average of the single Fourier transforms. Digital filtering techniques that utilize Fourier transforms, like the Wiener filter, are good for discriminating the signal from noise when there is a reasonably precise estimate of the frequencies contained in both the signal and the noise. A persistent problem with this technique, as pointed out by Naitoh (this section) is the decremental effects on high-frequency components when most of the area of the signal of interest is comprised of low frequencies. When this is true, the filter tends to see high-frequency components as similar to noise.

Development of pattern recognition techniques will have great impact on our future abilities to establish relationships between the EEG and complex behaviour. Any input that requires information processing must result in changes throughout the brain; there is certainly much evidence to suggest this. It is necessary to describe these changes as well as to get an overall picture of the relationships between them. It is particularly important to understand how these relationships change over time as a result of experience. Furthermore, it is extremely useful to be able to determine the degree to which a signal (within the brain) is like or unlike a predicted or theoretical signal.

A variety of pattern recognition techniques have been used with the EEG. I have been particularly interested in the utility of correlational techniques, such as the recognition index (RI) illustrated in Fig. 2, since they have the possibility of on-line application. Initial attempts were to simply cross-correlate a predetermined EEG pattern (template) with the ongoing EEG (Fig. 2).This procedure involves shifting the EEG against the template (or the template against the EEG) a predetermined number of increments of time after each correlation. The correlation coefficient ($r = Exy/\sqrt{Ex^2 Ey^2}$) utilized the entire distribution of voltages within the pattern as one variable. This did not work well since the effect of concurrence in time of fast frequencies was obscured by slower frequencies due to the total greater area occupied by the slower frequencies.

The next step was to divide the template into segments and correlate these segments separately, multiplying the correlations together for an index of the extent to which both of the segments in the template were present in the EEG (Fig. 3). This allowed a separation of segments containing the fast-frequency and slow-frequency components in the EEG (particularly the CNV). This procedure worked reasonably well; it reduced the number of false positives since a correlation coefficient of one of the segments of the template that was small reduced the resultant product of the coefficients. All negative products were ignored and plotted as zero.

The RI template may be an epoch of EEG data or a theoretical pattern. The advantage of this procedure is that a single-trial epoch of EEG, when designated as the template, can be matched against other single-trial epochs, giving an index of the goodness of fit for any segment of the EEG. The procedure, therefore, does not require repetitive samples of the same signal for recognition, nor does it require a temporal index of when the signal is occurring. A disadvantage of this technique is that it gives no indication of amplitude differences of signals that might have precisely the same pattern. I have therefore been experimenting with various methods of weighting the correlations with measures of area (fig. 4). I am also attempting to refine the template definition by increasing the number of segments of a

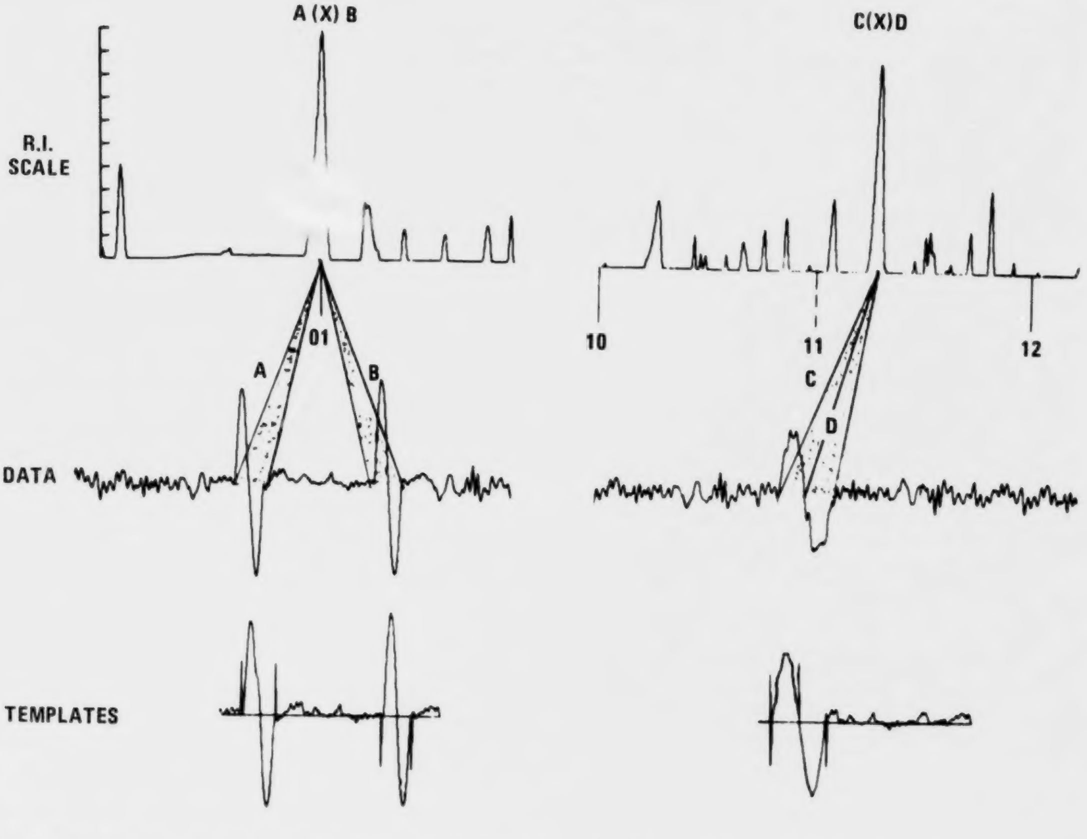

Fig. 2. Recognition index RI procedure using only two segments of the template. Note that when the segments of the template are separated in time, the RI is maximal (1.0) only when the data contain the same segments separated by the same interval. When the segments overlap, as in C and D, recognition is maximal when both segments overlap in a similar temporal relationship. A, B, C, and D refer to template segments. Numbers refer to magnetic tape blocks. Radiating lines enclose the segments of the data entering into the RI. Full scale of RI = 1.0.

template that can be independently manipulated for determination of the final recognition index. For example, the evoked potentials in a CNV may be much more "important" in some instances than the slow potential. Therefore, one may want to give them more weight in the determination of whether the EEG changes observed fit the pattern as defined. Since Fourier transforms and correlational analyses are closely related, the same procedure could be used with Fourier components, i.e., they may be iteratively computed as epochs of EEG are systematically shifted in time. However, one is again faced with the problem of how to define the pattern!

There are at least two conceptually distinct methods by which the pattern or template may be defined. It can be defined on the basis of a decision about what one is looking for, e.g., a CNV or a part-

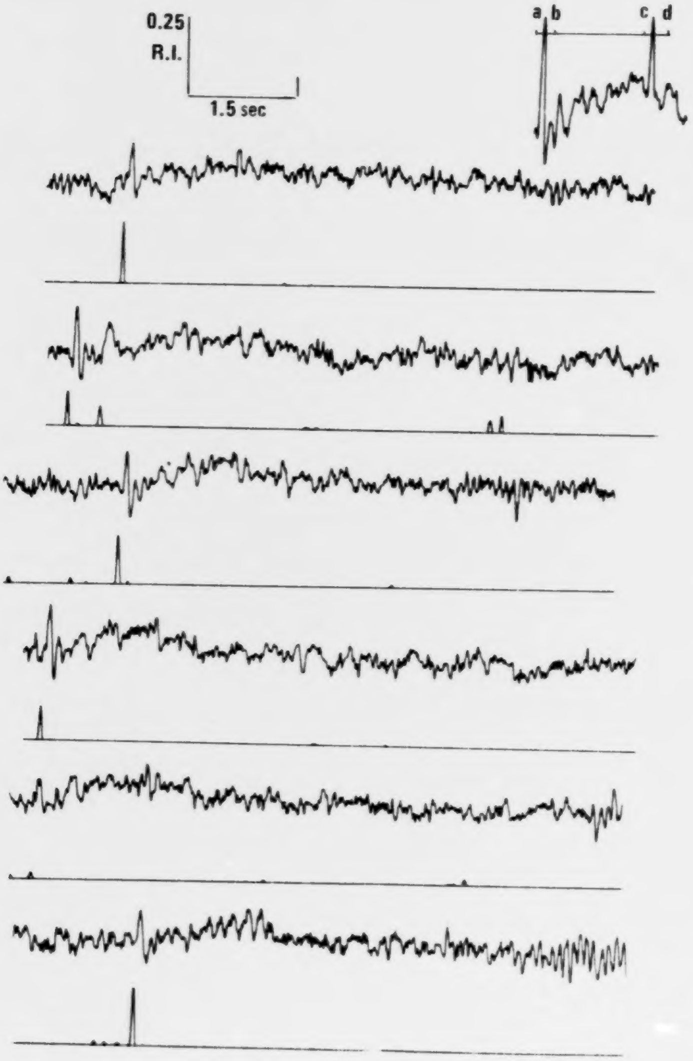

Fig. 3. Use of four segments in template shown at top, without inclusion of area as a factor in the RI. Note that the number of extraneous RIs is reduced from that shown in Fig. 2 and that the first line shows a trial in which the CNV is not obvious to visual inspection but is identified by the RI. Segments are ab, cd, bc, and ad. Each RI line refers to the trace above that line. Each EEG trace includes one CNV trial beginning coincidental with the related maximal RI on the line below each trace. RIs shown on each line correspond to the point in time at which the template is being matched to the data above that line.

icular configuration of EP components. The template may also be defined as that pattern, whatever it is, which dominates a given epoch of the EEG. In the procedure I use, an epoch of EEG in which I am interested is selected and the pattern is defined as a combination of subsets of that epoch. The template can consist of either a single trial or an average, or for that matter, some part of the spontaneous EEG. When selecting the pattern in this manner, the primary question of interest is the degree to which the pattern, as defined *a priori*, is extant in the EEG searched. However, the converse question could be asked (it is related to the second conceptual method for defining a template): Are there characteristic patterns in the EEG that are discoverable but not defined *a priori?* To give an example of the second possible method, one could take an arbitrary epoch of the EEG and do successive correlations of that epoch with the spontaneous EEG. The purpose would be to determine the goodness of fit at any particular time within the spontaneous epoch. That epoch could then be defined as a multiple or complex template by dividing it into two epochs (corresponding to what would be template subsets in a predefined pattern)

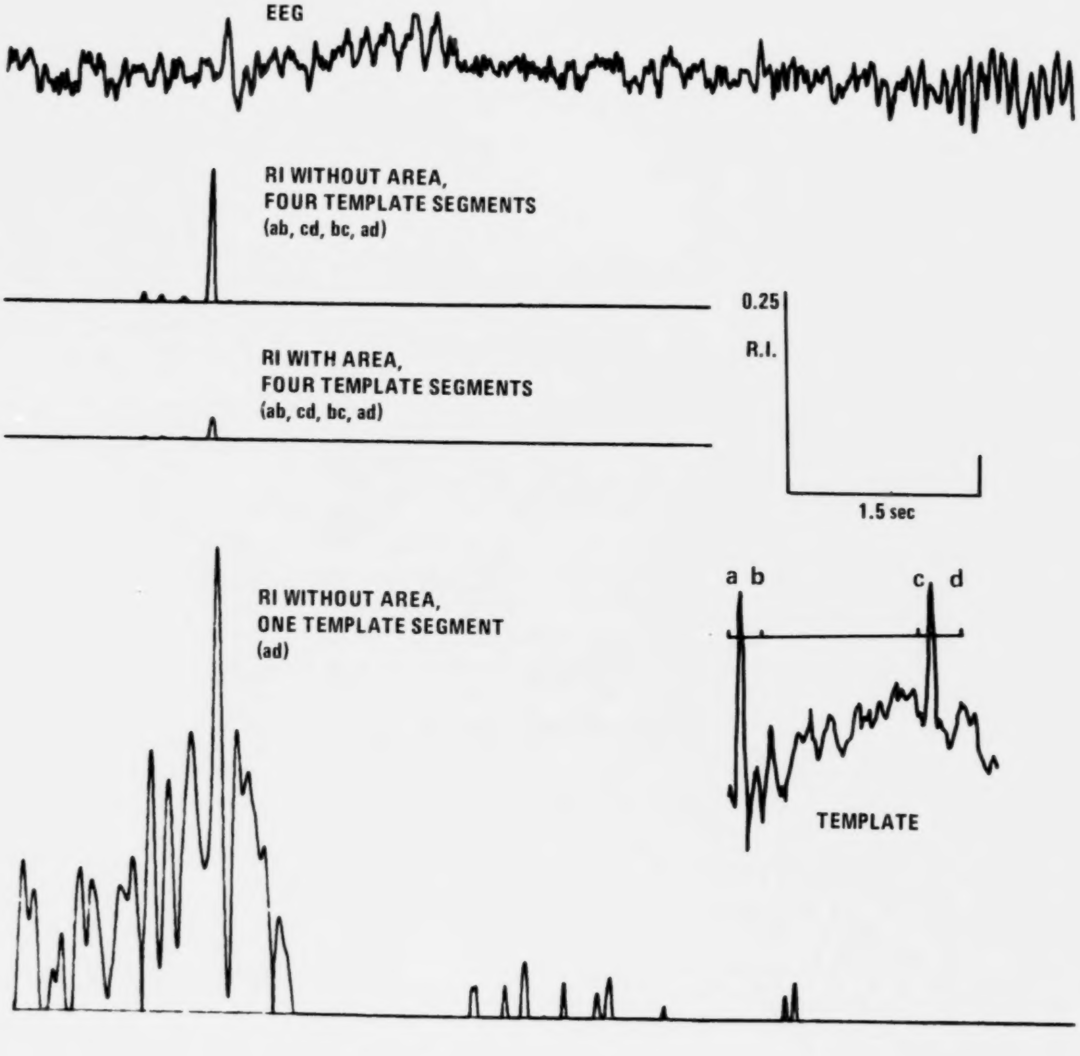

Fig. 4. Inclusion of area as a factor in the RI. If At *= area of template,* Ad *= area of data, and* Af *= area factor to be multiplied times RI, then for* $At \geqslant Ad$, $Af = Ad/At$ *and for* $At \leqslant Ad$, $Af = At/Ad$. *Thus,* Af *is always less than or equal to 1. For the four segments of the template shown, RI (with area) =* $r_{ab} \cdot r_{cd} \cdot r_{bc} \cdot r_{ad} \cdot Af$.

completing successive correlations for each of the template subsets. Resultant coefficients could be multiplied at each successive shift within the EEG searched in the same manner in which it is done when the template subsets are predefined. The purpose would be to determine the point in time within the spontaneous EEG when there is a best fit. Each of the subsets of the original template epoch could be systematically modified so as to produce "all possible patterns" that can be defined with a given number of subsets of the template epoch. For example, if there were two subsets, one subset could be defined as 0% of the epoch while the other is increased systematically from 0% to 100%. One of the subsets would be defined as 5% of the epoch while the other subset is systematically increased in increments of 5%, followed by the initial subset defined as 10% and the second subset increased in increments of 5%, etc. Presumably, the RIs that indicate the best fit throughout the EEG record will correspond to the dominant pattern. Unfortunately, this procedure requires a tremendous amount of computer time, which makes it currently impractical.

The RI, or some variant of it, may give information about topographic relationships between simultaneously recorded potentials (Fig.5). For example,

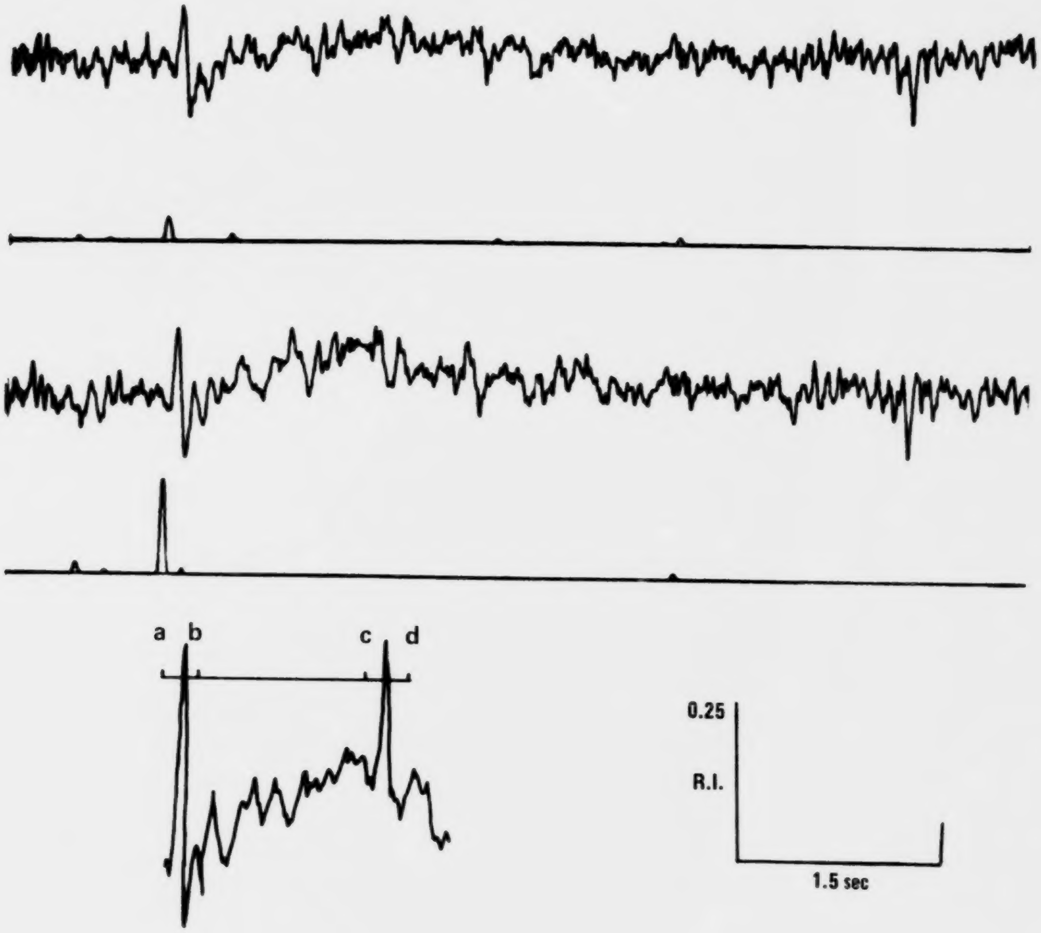

Fig. 5. Distributional information from the RI procedure. Upper trace shows T5 and lower trace T6, coincident in time for the same trial, trial 6, of a standard CNV paradigm. The template is the average CNV from Cz. Note that T6 is more like Cz than is T5 (area factor is excluded). Using Cz as a standard, distributional differences in shape of CNVs, with respect to the standard, may be described with the RI technique.

one could identify the EEG from a single site (perhaps the vertex) as a "standard" against which activity from all other sites is compared. A question of this sort could then be asked: To what extent is activity recorded from the frontal cortex more similar or less similar to vertex activity than it is to activity recorded from the temporal lobes? I have done this utilizing the averaged CNV recorded from the vertex as the template and have shown that the frontal CNV is more different from the vertex than are CNVs recorded from other sites.

The use of pattern recognition techniques applied to EEG data, whether they be variants of discriminant analysis, or the RI, or some other procedure, identifies limitations common to all measures. The limitation of all methods is the inability of these methods to identify patterns within the time domain without having *a priori* knowledge of exactly when these patterns occurred (or are to occur). This limitation makes it virtually impossible to study the EEG related to thinking processes that are not time-locked to input or output. Consequently, our understanding of the relationship of ERPs to complex human thinking processes is so limited it can only be described as trivial. We must find methods to go beyond event-locked potentials if we are to ever have an understanding of ERPs, and more importantly if we are ever to have an understanding of spontaneous thinking processes.

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X. THEORETICAL APPROACHES AND MODELS

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A THEORETICAL FRAMEWORK FOR EVOKED POTENTIAL AND SLOW POTENTIAL RESEARCH

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Introduction

The chapter which follows is based on several distinct sources of information, although it has often been necessary to blur the distinctions to avoid overlap and repetition. The first source was a correspondence conducted prior to the EPIC IV Congress in which a number of the participants exchanged views on the necessity for a theoretical model, or models, in this field of research and the form that such a model might take. The second source was a series of meetings during the Congress by the subgroup concerned with this topic. This was followed by a plenary session on "Theoretical Models" at which members of the subgroup presented their respective views and the matter was discussed by Congress participants as a whole. Finally there was a series of written contributions submitted either as part of the prior correspondence or subsequently in support of various arguments advanced.

To provide a coherent account of such diverse material is perhaps more than can be expected. However, as an aid to the reader, an attempt has been made to impose a certain minimum structure on the arguments used. Some points have been summarized or paraphrased, but extensive use of direct quotations has been made where appropriate. Where contributors have, following the congress, reformulated their views and arguments into a coherent text, these papers have been included at the appropriate point within this section. One paper, entitled "A biomodal slow potential theory of cerebral processing," originally prepared by Cooper, McCallum and Papakostopoulos for the Symposium on Cerebral Evoked Potentials held in Brussels in 1974, was circulated prior to the Congress as a basis for discussion. This is included in full together with an account of the various comments, criticisms and lines of argument which it generated.

Because of the range of disciplines involved, the diversity of solutions proposed and the varied lengths of contributions, the remainder of the section has been divided into a series of subsections outlined at the end of this introduction.

The Need for a Model

It may be asked why, after three international congresses on ERPs have apparently seen no necessity to discuss the subject of "Theoretical frameworks" or "models," there now existed a need for such discussion. Although science depends upon the steady accumulation of the results of observation and experiment, mere accumulation is of limited value. What is also necessary is insight to discern relationships expressable as simple general laws. This is essentially no more than a fundamental restatement of what science is about. In the field of slow potential research the gap between the acquisition and interpretation of data has steadily widened. For example, we have spent some thirteen years or more studying the CNV, which was responsible for initiating this series of congresses. During that time there has been a steady accumulation of important facts, but at the end of it we still have a relatively poor understanding of what this shift of potential represents in terms of human function. Evoked potentials have an even longer history of a similar kind and the Bereitschaftspotential and, to a slightly lesser extent, those potentials which accompany the execution of movements, stand in much the same position.

Largely as a result of this failure to raise our experimentation beyond the phenomenological level, practical applications have remained remarkably few in number for effects which were hailed as being among the most significant in human neurophysiology for

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some decades. It would be wrong to imply that no progress has been made, but the return to be found from the enthusiastic pursuit of new phenomena and from accruing a huge store of largely unrelated facts is rapidly diminishing.

It is both the strength and weakness of our common field of research that it spans almost the whole of the neurosciences both in the disciplines from which its investigators come and in the directions in which relationships with the basic electrophysiological phenomena are sought. The strength of a "tool" which unites researchers from the fields of Physiology, Psychology, Anatomy, Neurology, Psychiatry, Biochemistry and Pharmacology is obvious. However, it has also the disadvantage that it tends to encourage the intensive pursuit of a variety of specialized relationships between the electrophysiological phenomena and such diverse entities as cognitive states, anatomical pathways, pathological processes and physiological mechanisms. This would in itself be no bad thing if it were not for the rather poor level of interdisciplinary communication that has tended to exist so far. Fortunately EPIC IV itself has taken a large step towards crossing these communicative barriers. What is now required is an exercise in synthesis.

To be effective it would seem that such a synthesis should lead to the formulation of a theoretical framework, model (or models), which permit the integration of our various data into a more general notion of brain systems and their relationships to behaviour. The end-product should have the following characteristics:

1. It should be capable of assimilating the existing body of scientific data.
2. It should generate further testable hypotheses.
3. It should result in an increased understanding of the relationships that exist, of the systems and mechanisms which these relationships imply, and of the features that differentiate these systems and mechanisms from others.

What Kind of a Model?

Before attempting to answer this question it is necessary to examine what we mean by the term "model." For some it may imply several pages of flow diagrams, some may prefer to work with analogs, some may think in terms of behavioural black boxes, some prefer to delineate physiological systems and mechanisms while others wish to express their framework in mathematical terms. Ultimately all are attempts to impose a form upon that area of implicit assumptions which lies behind the work of every researcher. It is an area where fact shades into speculation, with the result that many of us are reluctant to air such private speculations in public, being all too painfully aware of the gaps in both the evidence and the logic. However, it would seem important that we at least attempt to identify the common ground that exists in our diverse formulations. We ought also to be assembling the currently available evidence in a way which reveals where the major gaps in our structure lie and perhaps enables us to state more clearly how the structure we are building differs from other structures.

We have already touched upon the strengths and weaknesses of our interdisciplinary approach. Our first problem becomes one of identifying our common ground and the source of the differences that exist. What we have in common in this field is a basic methodology for recording event related electrical changes from the brain, together with the body of electrophysiological data produced by that methodology. Divergence occurs because, in trying to integrate this data within a coherent theoretical framework, we seem to take a number of very different starting points. While this may be a healthy state of affairs we should examine more carefully the extent to which it facilitates or impedes our attempts at synthesis and perhaps interferes with our attempts at communication.

Analysis of preliminary correspondence and discussion, and indeed of the literature and general congress contributions, reveals that there are at least three distinctly different starting points. In the remainder of this chapter we will endeavor to outline these, to examine the extent to which they can be reconciled with one another and then to turn to the data itself and to take a critical look at what constraints it imposes on our framework.

"The Behavioral Approach" described by Dr. Loveless provides a starting point. From the perspective of experimental psychology, Dr. Loveless perceives the basic objective as one of integrating event related potential data into existing behavioural theory and relating it to existing psychological constructs.

The second approach stems from researchers whose anchors are in physiology and chemistry, represented in this section by Drs. Skinner and Marczynski, respectively. The basic objectives are to build bridges between molar and molecular processes–to approach macropotentials and their implications from the unit level of activity, from functional anatomy, biochemistry, and neuropharmacology.

The third approach takes macropotentials themselves as a startingpoint and looks both outwards and inwards. This approach, as described by Dr. Papakostopoulos, seeks to understand the data in relation to existing knowledge about neuro-anatomy and cellular neurophysiology, while at the same time it tries to relate the whole to systems, mechanisms and, ultimately, to the direction of behaviour.

In the last analysis the building blocks of our model must be macropotential data. We must identify the key characteristics of the data that need to be accounted for by any theory that is to emerge as a useful predictor of behaviour and a generator of testable hypotheses. A crude chronological division has been chosen to deal with the phenomena themselves. Thus the period of time which precedes voluntary actions is considered first. Dr. Deecke discusses the Bereitschaftspotential or Readiness Potential that is associated with this preparatory period, and the slightly later group of potentials which occur when movement is executed. Dr. Ritter then examines the relationship between ERPs and consciousness, with particular reference to those evoked potential components which follow the onset of an external signal and extend over a period of three or four hundred milliseconds. This is followed by a look beyond 400 msec by Dr. Näätänen to the characteristics of the slower and sustained potential changes such as the CNV, and some general comments by Dr. Cooper. The "Bimodal model," which was primarily - although not exclusively - based on SP data, is included at this point together with its discussion. The section ends with a discussion of the major issues raised.

THE BEHAVIORAL APPROACH

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I share a feeling of disappointment at the relative absence of theoretical discussion at recent conferences, particularly about the relationship of the CNV to those psychological variables to which it appears to be sensitive. This is perhaps a reaction against early speculation about the "psychological correlates" of the CNV, but seems to have reached a point where people are unwilling to say anything at all. There is a danger of being too solemn about theory. Even the quest for psychological correlates may have been useful in suggesting variables worth investigating. I do however agree with Donchin et al. (1972) that this type of theoretical interpretation, if it deserves to be called theory at all, is not likely to take us far in determining the functions of ERSPs. Concepts such as "attention" are not only ill-defined, but also of too high an order. Luria (1973), discussing the localisation of function in the brain, remarked on the ambiguity of the term "function", which may be used to refer either to the elementary function of a particular tissue, or to a complex process such as digestion which involves a number of component systems. It seems equally foolish to attempt to identify a complex process such as "attention" with a bioelectric response of a limited brain area.

One of the factors impeding progress in the construction of "theoretical models" in this field emerged in our preliminary correspondence. We found that we were to some extent talking at cross-purposes. We were talking about different approaches to constructing them. For example, I would epitomize the differences between McCallum and myself as being that my approach is one of physiological psychology whereas his is one of psychological physiology. The latter approach tends to take a physiological phenomenon as primary, to set up general hypotheses about its function and then seek to test these by devising suitable behavioral situations.

It is, of course, an entirely respectable strategy to devise fresh paradigms when faced with a new phenomenon. However, I think that we should heed what Sutton said some years ago, namely that pioneers in ERSP research tend to behave like explorers facing an uncharted continent. The point is that although it is to be expected that a new phenomenon will excite fresh speculation, it is necessary and proper to attempt to relate it to what we already know. The appropriate level of 'psychologizing' is surely, as Vaughan (1969) has suggested, to attempt to specify those component processes which contribute to performance in the task used to generate ERSPs. In this respect CNV research has unfortunately proceeded in virtual isolation from relevant areas of psychology. When I first entered this field, I was astonished to find that although the standard CNV paradigm was that of warned RT, virtually no use was being made of previous research on this task. It would be absurd to pretend that 'knowledge' in this field amounts to a body of well-tested theory, but equally absurd to proceed as if the efforts of psychologists over the past hundred years have taught us nothing. The RT literature is voluminous and of very uneven quality, but it contains at least some well-tested generalizations – for example, the effects of foreperiod manipulation which I have replicated in some of my own research. While there is no existing theory which adequately covers all the established facts about reaction tasks (Broadbent 1971), disagreements may cover substantial areas of agreement, and available models have considerable heuristic value. Yet with a few honorable exceptions, CNV researchers proceed as if such models do not exist. I have found it fruitful simply to replicate some well established behavioral phenomena and to see what happens to ERPs when one does this. I sense from the exciting accounts of sequential effects reported elsewhere in this volume by Squires and Squires that others too are following this course.

The situation is not much better in relation to classical conditioning. Early reports on the CNV made considerable use of conditioning concepts, but this practice seems to have fallen away. I wonder whether this may be due to a mistaken interpretation of the relationship between conditioning and RT paradigms. For instance, Rebert and Knott (1970) note that the two paradigms are alike in that the conditional stimulus comes to have cue significance similar to that of the RT warning signal, but consider them different in that "during conditioning, the conditioned response comes to precede the unconditional stimulus, i.e., the animal does not inhibit the required response until onset of the second stimulus, as is true in the reaction time experiment". This appears to involve confusion of the conditional and unconditional responses. In the Pavlovian situation, some components of the unconditional response, such as chewing, do not precede the second stimulus. Other components, such as salivation, appear also in the conditional response, and are most clearly characterized as anticipatory or preparatory. In the RT situation, therefore, the analogue of the conditional response is not the reaction to the second stimulus, but the development of "preparatory set" during the foreperiod.

I do not altogether agree with Donchin's strictures on the mixture of RT and conditioning terminology, since this may facilitate drawing upon two somewhat distinctive research traditions. We not only stand to lose whatever positive gains have come from the study of conditioning, but risk falling into the numerous methodological pitfalls which have been discovered in that field. I am thinking particularly of our addiction to short inter-stimulus intervals. It may be true that in classical conditioning a short interval is 'optimal' in the sense that it produces the most rapid conditioning, but the short interval may not be optimal for purposes of investigation. The advantages of delayed conditioning procedures were recognized long ago in Pavlov's laboratory, not least that changes due to conditioning can be studied without the necessity of introducing test trials on which the unconditional stimulus is omitted. This practice was not adopted by Western investigators, who have only recently come to realize that the use of short ISIs has led to the confusion of several responses. Thus in eyeblink conditioning, the long-latency closure that develops in anticipation of the UCS must be distinguished, not only from voluntary blinks, but also from short-latency responses to the CS. These distinctions are difficult to make when the ISI is short. Similarly, in autonomic and EEG conditioning, a long-latency anticipatory response can be clearly differentiated from the short-latency orienting response only when a delayed conditioning procedure is used. It is very evident from the summary by Martin and Levey (1969) that this lesson has been painfully learned. Is it hubris or historical ignorance which leads us to suppose that the CNV paradigm will be exempt? Results obtained by the handful of investigators who have used long ISIs suggest that it is not. Short ISIs are undoubtedly more convenient to use, but are likely to produce a mix of potentials. It is then hardly surprising that terminal CNV amplitude and RT are sometimes dissociated, or that it is difficult to determine CNV function.

Martin and Levey point out that since the orienting response, anticipatory response, and response to the UCS all change in the course of conditioning, it is rather illogical to refer to any one of them as *the* conditional response. I wonder whether we have not reached the point where referring to any negative potential that develops during the ISI as 'the CNV' is not a positive impediment. I have in mind, for example, the question whether the CNV is contingent on a motor response. I do not doubt that 'non-motor tasks' produce *some* negative potential, but I suspect that in many cases it may be an orienting potential because the waveform often has a convex dome shape, with no terminal rise. In my own research I have been impressed by cases in which I have *failed* to observe a clear-cut anticipatory response, i.e., in a signal-detection task with delayed verbal response and in an RT task performed under 'sensory set', when muscular preparation was discouraged. Under long ISI conditions, I have seen a good anticipatory response only when a vigorous motor response was required. I am also impressed by the relationship between CNV and anticipated force of movement.

A clear distinction between 'motor' and 'non-motor' tasks may, of course, be difficult to draw. Nearly all tasks have some motor component, at least in the form of postural adjustment or change in muscle-tension. However, the distinction is not trivial: one of our outstanding failures is the unresolved relationship between the CNV and Bereitschaftspotential. McAdam et al. (1969) first pointed out the morphological similarity between the readiness potential and the anticipatory potential recorded under long ISI conditions. Subsequent research suggests that the two potentials are functionally related–i.e., both are concerned with motor preparation, and are similarly affected by incentive. The outstanding difficulty in sorting out their relationship has been the difference in scalp distribution. If one assumes that the conventional CNV is the sum of a Bereitschaftspotential and a negative frontal wave, the difference in midline topography is easily accounted for (Gaillard 1976). The difference in laterality was more puzzling until Syndulko and Lindsley (1977) suggested that it might result from insufficient care to limit response to one muscle group in CNV experiments. This led to the suggestion that the topographical problem might be resolved if the Syndulko and Lindsley experiment were repeated with a longer ISI. The elegant experiment by Rohrbaugh, Syndulko and Lindsley (1976), in fact, provides a very effective resolution. I now take it as established that the CNV consists of two components which are functionally, morphologically and topographically distinct, and that the second of these *is* a Bereitschaftspotential.

In the belief that questions about the function of ERSPs are best approached through a process analysis of the CNV paradigm, I would like to present an attempt to do this.

A Tentative Process Analysis of the Basic CNV Paradigm

While it seems sensible to distinguish evoked potentials and ERSPs, an adequate analysis of the CNV paradigm must include the functions of both evoked and motor potentials. For the sake of argument, I assume that the Picton and Hillyard (1974) analysis of the auditory EP is broadly true. This two-stage model first posits a 'compulsory' feature analysis of sensory input. This first stage may include 'novelty detectors' that generate an output when any feature changes. On the basis of this initial analysis, signals may be selected for further processing by comparison of current input with memory models of expected or significant stimuli. In the present instance, therefore, these mechanisms only generate an output when an event is differentiated from background activity and identified as the warning signal.

This identification must be followed by the selection of appropriate action, which presumably involves the establishment of routines for recognizing and responding efficiently to the imperative signal. Efficient response will depend upon the use of information about the probable time of occurrence of the imperative signal. The formation of complex programs of activity is characteristic of prefrontal cortex. This 'executive' function is, therefore, probably associated with the slow negative potential which follows S1 and appears to be frontally-dominant. This potential peaks in about one second and then decays over about five seconds – a time-course similar to that for changes in heart rate and alpha desynchronization (commonly regarded as components of the orienting response). Identification of the slow potential as such a component is supported by its appearance as a response to unpredictable changes in nonsignal stimuli and by its rather slow habituation to signal stimuli. The orienting response is reputed to be a frontal lobe phenomenon.

An important function of the orienting response is to increase the probability of detecting subsequent stimuli. This function appears to be exercised through the control of sensitivity, which follows a timecourse similar to that of the slow potential, i.e., increasing shortly after the warning signal and then declining over a few seconds. The amplitude of the potential appears to depend on the intensity and modality of the warning signal. Since variation of sensitivity will alter the rate at which evidence of the imperative signal will become available in reaction tasks, it seems likely that this 'sensitizing' mechanism mediates the effects upon RT of warning signal characteristics and of foreperiod duration over the first few seconds following the warning signal.

The 'orienting potential' is distinguished from the rising negative potential that develops in anticipation of the imperative signal when the subject has some certainty about its time of occurrence. The most obvious illustration of the effect of temporal uncertainty is the development of a marked anticipatory potential when the foreperiod is of constant rather than variable duration (cf. Type A and B CNVs, McAdam 1969). Such a potential may also be seen with a variable-foreperiod paradigm when presentation of the imperative signal is probable, notably at the longest foreperiod being used. When the foreperiod varies over a short range, the potential rises steadily over this range to reflect the increasing conditional probability that response will be required. When the time of the imperative signal is known, the amplitude of the potential is affected by instructions stressing speed of response through muscular preparation. The anticipatory potential therefore occurs when the subject uses information about the probable time of imperative signal occurrence to produce a brisk motor response. There seems to be general theoretical agreement that RT reflects the time necessary for unreliable evidence of the occurrence of an imperative signal to accumulate to a point where a particular response can be selected with an acceptably low rate of error. The further time taken to launch the response is presumably minimized by lowering a response threshold. This process is presumed to be the functional correlate of the anticipatory potential.

Several authors (cf. Rebert and Tecce 1973) have argued against such an interpretation on the grounds of dissociation between RT and CNV amplitude. Apart from the ambiguity of 'CNV amplitude', no one has ever claimed that RT is determined only by effective preparation. The observed distribution of RTs is generally agreed to be a convolution of different distributions reflecting the different processes involved in the task. Several authors (e.g., Hohle 1965) explicitly analyze the distribution into components representing preparatory set and decision time. Dissociation has commonly been observed with a short constant foreperiod wherein temporal certainty is high relative to the time for which preparation can be maintained. Under these conditions, a practiced subject is likely to produce a fairly stable level of preparation and RT is likely to be appreciably affected only on a few trials when the subject anticipates or is unready. This does not mean that preparation is unimportant – how else do we explain the persistent difference between warned and unwarned RT? What it surely means is that under these conditions the proportion of trial-to-trial RT variance attributable to fluctuations in preparation is small relative to the effect of variation in decision time.

This argument might be supported by evidence of substantial correlation between RT and the latency of late EP components if it could be confirmed that some of these components precede the initiation of motor response, as Vaughan and Ritter (1973) have claimed. (It might then be interesting to look at the multiple correlation of these latencies and anticipatory potential amplitude with RT). None the less, some components which may be related to stimulus identification occur after the subject has responded. Practiced subjects commonly report that they have reacted before they are aware of the stimulus. In a simple RT task, the subject may achieve speed by reacting to *any* appreciable change in input (subjects trying to produce a fast response to a visual stimulus readily respond to an accidental noise) – i.e., the subject responds on the basis of fewer features than he needs for confident identification of the stimulus. In choice RT, this finding may be related to the distinction between "fast guesses" and true discriminations (Ollman 1966). Such heterogeneity of response would help to explain the dominance of decision-time.

I put forward this analysis more as an indication of the sort of model I would like to see than in the belief that it is adequate. If this model seems too much of a "personal ivory tower," the reason is that the model is limited to effects obtained with long foreperiods, although there are a number of obvious links with results obtained with the conventional paradigm. There is a good deal of evidence supporting a distinction between frontal and central potentials, and between 'early' and 'late' CNV. Thus, an obvious prediction is that amphetamine affects the orienting potential (it would be interesting to use non-signal stimuli). The 'early CNV' also seems to be particularly vulnerable to distraction (see Loveless, this volume). On the other hand, distraction does not appear to affect RT, though the maintenance of performance under distraction may require increased effort. 'Effort' also seems to be implicated in the effect of sleep deprivation on the 'late CNV'. Pribram and McGuiness (1975), whose distinction between 'arousal' and 'activation' seems related to that between orienting and anticipatory effects, have felt it necessary to involve effort as a third variable. Does anyone have a correlate for effort?

Finally, little systematic study of individual differences in the CNV has been made, despite a widespread impression that there are characteristic differences in its form. Donchin's essay in factor analysis (1972) tends to confirm the distinction between 'Type A' and 'Type B' CNVs. This morphological distinction may depend, in part at least, on the relative amplitude of orienting and anticipatory potentials, and might form a basis for theoretical interpretation, perhaps related to the work of Soviet factor analysts (Nebilytsin 1972) who make considerable use of concepts drawn from conditioning theory.

In summary, I seek a model of what is going on in an individual's head when he is performing in standard behavioral paradigms. To construct such a model, we must combine what we know about all the event-related potentials that occur in the task situation. We have been urged to move on from mere phenomenology. The time has come to move away from research subgroups clustering around discrete physiological phenomena and failing to communicate with one another. The work based on information processing presented at the congress and some of the recent research on slow potentials suggest that we may now be in a position to give a coherent account of at least one standard task. Given that this sort of integrative model building is possible, I would subscribe to effort being invested in building models of a few well chosen tasks.

A NEUROPHYSIOLOGICAL MODEL FOR REGULATION OF SENSORY INPUT TO CEREBRAL CORTEX[1]

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Desynchronization of the EEG, enhancement of sensory evoked responses and negative or positive shifts in slow potentials are electrical events in the human cortex that have been associated with arousal and selective attention. These three types of electrocortical events have been shown to be regulated in animals by both the mesencephalic reticular formation (MRF) (Rossi and Zanchetti 1957) and the mediothalamic-frontocortical (MT-FC) system (Skinner and Lindsley 1973). The MRF and FC are known to converge upon the thalamic reticular nucleus (R) (Scheibel and Scheibel 1966, 1967a; Millhouse 1969), a perithalamic structure, which presumably integrates the convergent inputs and then projects systematically to the interior of thalamus (Scheibel and Scheibel 1966, Jones 1975). Evidence, reviewed below, suggests that FC and MRF influences on R regulate various inhibitory gates on the thalamic relay nuclei and, by this mechanism, continuously control the pattern of sensory input to cerebral cortex. I propose that this neural mechanism, identified in the cat brain, mediates the processes of both general arousal and selective attention because neurophysiological manipulation of the system not only alters the three types of electric activities associated with these processes, but also effects the expected behavioral changes.

EEG desynchronization, modulation of slow potentials, and enhancement of sensory evoked potentials are discussed in the next three sections, respectively. In each case, the model will be used to explain the regulation of the electrical activity. Implications of the model for the regulation of human-event-related potentials will be discussed in the final section.

EEG Desynchronization: Reduction in Phasic Thalamic Inhibition

Mechanisms of EEG Synchronization

To understand the process of EEG desynchronization, one must understand how synchronous activity itself occurs. Recruiting and augmenting responses produced by 8- to 12-c/sec medial and lateral thalamic stimulation, respectively, have been used as experimental models for EEG cortical rhythms since discovery by Morison and Dempsey in 1942. Both electrically induced responses show systematic increases and decreases in amplitude with successive stimulation in a low-frequency train, and thereby produce the fusiform or spindle shape of spontaneously occurring EEG rhythms characteristically recorded from the cortex of a quiescent or inattentive animal. Recruiting responses produced by *medial* thalamic stimulation were thought to be the better model for spontaneously occurring EEG spindles for they interacted with natural waves in such a way as to suggest that both rhythms shared common pathways (Dempsey and Morison 1942). Also, both recruiting responses and spontaneous spindles had primarily frontal distributions in the cortex, whereas augmenting responses did not (Morison and Dempsey 1943). Augmenting responses produced by *lateral* thalamic stimulation (i.e., sensory and motor relay nuclei) were found to be independent of frontally projecting spontaneous EEG rhythms and later were shown to have profiles of laminar activity in the cortex different from those of recruiting responses (Spencer and Brookhart 1961).

Schlag and Villablanca (1967) showed that waveform could not serve as a criterion to distinguish between recruiting and augmenting responses. Recruiting responses elicited by medial thalamic stimulation were found to have positive-negative waveforms in the hidden region of the orbital cortex in cats, and augmenting responses evoked by lateral thalamic pulses manifested their positive-negative responses in the more accessible cortical convexity. These authors also pointed out that positive-negative cortical projection fields of *both* recruiting and augmenting responses were surrounded by large zones in which only monophasic negative responses were recorded.

The best criteria for distinguishing between recruiting and augmenting responses are observed

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[1] Supported by a grant from the National Institutes of Health, HL-17907.

effects on behavior. Frontally projecting spontaneous EEG rhythms are invariably associated with inattentive behavior. Electric 8-c/sec stimulation of the medial thalamus completely disrupts bar-pressing behavior and renders the animal inactive. At lower intensities, such stimuli produce a deficit in single alternation performance (King and Skinner 1975). Stimuli that elicit augmenting responses have, in contrast, no detectable effect on behavior. It is not surprising that medial and lateral thalamic stimuli have different behavioral effects because the medial thalamus receives intrinsic inputs from other thalamic nuclei and the lateral thalamic nuclei receive extrinsic projections from the periphery and other sources outside the thalamus. Thus recruiting and augmenting responses appear to be mediated by anatomically distinct systems that subserve different behavioral functions. It is important to realize that different mechanisms exist for different types of cortical EEG rhythms because false controversies have arisen when EEG synchronous activities were posited to reflect a unitary process (see Skinner and Yingling 1977; Skinner 1971a).

Role of the Reticular Nucleus in Phasic Thalamic Inhibition

Moruzzi and Magoun (1949) demonstrated that electric stimulation of MRF would produce behavioral arousal, desynchronization of spontaneous EEG, and abolition of recruiting responses elicited by medial thalamic stimulation. Skinner and Lindsley (1967) showed that blockade of the MT-FC system at any point would also abolish recruiting responses and spontaneous spindles (produced by MRF lesion) *in the thalamus* as well as in the cortex. This latter result suggests that an *extrathalamic* circuit is necessary for the generation of these forms of thalamic synchronization. Villablanca and Schlag (1968) confirmed that blockade of the pathway between the medial thalamus and frontal granular cortex abolished spontaneous thalamic spindles in the partially decorticate *isole* preparation. They also found that total thalamic isolation resulted in a modified recurrence of thalamic synchronization. This suggests elements entirely *within* the thalamus can support synchronous rhythms. It would be prudent not to identify preisolation thalamic spindles with those recorded in the isolated thalamus because (1) only the criterion of waveform is employed and (2) extrathalamic circuits are clearly required in the preisolation condition and not in the latter. How then is one to distinguish among the various forms of thalamic synchronization?

Feedback from inhibitory interneurons upon the thalamocortical cells may be required to produce neocortical rhythms. This hypothesis is based on observations (Purpura and Cohen 1962, Andersen and Eccles 1962) during synchronization that long-duration inhibitory postsynaptic potentials occur between action potential bursting intervals of thalamocortical neurons and produce a burst-pause firing pattern in thalamic cells during each cycle of rhythmic spindle activity (Purpura and Cohen 1962, Andersen and Eccles 1962, Purpura et al. 1966, Andersen 1966, Andersen and Anderson 1968). The questions that arise are: (1) where are the interneurons? and (2) are they the same for all types of synchronization? Evidence reviewed by Andersen and Anderson (1968, p138) suggests that interneurons, at least for some types of rhythmic responses, are distributed locally throughout the thalamus, much like Renshaw cells are distributed locally within or near ventral root motoneurons in the spinal cord. The evidence, however, is not conclusive.

Recent studies have indicated that during synchronization, cells in the thalamic reticular nucleus (R) fire in long high frequency bursts when cells in nearby thalamic nuclei are silenced, presumably by long-duration inhibitory postsynaptic potentials (Massion 1968, Massion and Rispel-Padel 1972, Schlag and Waszak 1970, 1971, Filion, Lamarre, and Cordeau 1971, Lamarre, Filion, and Cordeau 1971, Frigyesi 1972, Frigyesi and Schwartz 1972). Yingling and Skinner (1975) showed that the envelope of the post-stimulus-time histogram of R-units responses to medial thalamic stimuli were identical in wave-shape, latency, and duration to the characteristic inhibitory post-synaptic potentials routinely observed in thalamic neurons during recruiting responses. They also found that lateral thalamic stimuli do not drive the same R-units that respond to medial thalamic pulses. *Thus, fairly strong evidence suggests that R is the site of inhibitory interneurons that mediate recruiting responses.* The location of inhibitory neurons for augmenting responses is unknown; the interneurons may be locally distributed throughout the thalamus or may be in regions of R not yet explored. It is certain, however, the interneurons for augmenting and recruiting types of synchronous activities are not located in the same cell groups.

The Mechanism of Regulation of the Recruiting Type of Thalamic and Cortical Synchronization

Schlag and Villablanca (1967) showed in thalamectomized cats that 8-c/sec stimulation in white matter produced long latency responses in frontal cortex, which recruit in amplitude similarly to cortical recruiting responses. Skinner and Lindsley (1967) showed that blockade in the pathway between MT and FC, i.e., in the inferior thalamic peduncle (ITP), abolished recruiting responses in the frontal lobe. Thus, the burst-pause pattern of activity originating in MT appears to be sufficient to evoke long-latency recruiting responses in FC; anatomical evidence supports this physiologically inferred pathway from MT to FC via ITP (Scheibel and Scheibel 1967a).

ITP blockade could also interrupt a descending projection from FC to R, a disconnection that would abolish cortical and thalamic recruiting responses by eliminating the drive on inhibitory interneurons that give rise to the burst-pause pattern of activity in thalamic cells. Steriade and Wyzinski (1972) have shown that FC stimulation produces very short-latency responses in R units, a result consistent with a monosynaptic projection from FC to R. This FC-R projection is supported by anatomical evidence, which shows that FC axons provide innervation of the anterior neuropile region of R (Scheibel and Scheibel 1967). The FC-R pathway, like the MT-FC one, also travels in the ITP. Thus ITP blockade interrupts both inputs and outputs of FC in its extrathalamic circuit connecting MT to R.

ITP blockade prevents MT stimuli from evoking unit responses in R and so does MRF stimulation (Yingling and Skinner 1975). Thus, a third alternative is that ITP blockade disrupts an FC-MRF-R circuit and has the same affect on R cells as MRF activation (i.e., disinhibition of the MRF). However, since ITP blockade eliminates thalamic recruiting responses and spontaneous spindles in an MRF lesioned animal (Skinner and Lindsley 1967), this last alternative appears to be ruled out and leads us to believe that the FC projection to R is independent of MRF. Several reports, based on Golgi-stained material, trace projections of the ventral leaf of the ascending MRF through the subthalamic and hypothalamic fields into the vicinity of the rostral thalamus and R (Scheibel and Scheibel 1967a, Millhouse 1969). Thus, some anatomical evidence supports the existence of an MRF-R projection that is independent of the FC-R pathway.

The regulation of R by MRF and FC appears to control the pattern of thalamic inhibition that underlies the recruiting type of EEG synchronization. FC has a *phasic excitatory affect* on R cells that lasts for 100 msec following activation by an MT stimulus, whereas MRF has a *tonic inhibitory influence* on the same R cells that lasts for 20 to 30 sec (Yingling and Skinner 1975). Thus, *desynchronization of the recruiting response can be produced by either inhibition of R units by MRF or blockade of pulsatile excitation of R units from FC.*

Slow Potentials Also Reflect Dual Regulation of R by MRF and FC

Cortical Slow Potentials

Arduini et al. (1957) first showed that a negative slow potential (SP) shift could be produced on the surface of the frontal cortex in a cat by stimulation of sensory nerves or the MRF. SPs and EEG desynchronization persisted for many seconds following the stimulus. The effect of drowsiness, a condition related to a decrease in MRF activation level (Jouvet 1967), has been shown in animals to result in a tonic frontocortical slow potential of opposite polarity (i.e., surface positive) (Caspers 1963, 1965). Thus, it appears that conditions associated with an increased tendency for EEG synchronization in neocortex result in SPs on the frontal lobe that are *positive* in polarity and conditions that reduce EEG rhythmic activity result in *negative* shifts.

Surface SPs can also be produced in FC by a warning signal associated with a meaningful expected event. Walter et al. (1964) first demonstrated that a tonic negative slow potential, contingent negative variation (CNV), was produced in the frontal region of humans during conditioned expectancy. The CNV has been implicated in a cerebral process that appears to be distinct from general arousal usually associated with a mesencephalic reticular mechanism. Skinner (1971b) has implicated the MT-FC system of the cat in the generation of such neocortical expectancy waves. Slow potentials, elicited by a warning tone that signaled the onset of electric shock, were evoked in FC and motor cortex, but only FC responses were abolished by ITP blockade.

Slow Potentials in R

Extracellular positive SPs have recently been recorded in R following (1) a tone reinforced by cutaneous shock and (2) an electric stimulus in MRF (Skinner and Yingling 1976). Both types of R responses were found to mirror exactly those recorded in FC, except that the responses were positive in polarity in R rather than surface-negative as observed in FC. By manipulating the parameters of the stimulus situation, *conditioned* responses in both locations could be modified. Changes in the interval between tone and shock, introducing an unreinforced tone of different frequency, or massing trials with a mean of 30 sec rather than 3 min, all modified the responses by affecting peak latency, amplitude, or other aspects of the waveform. All modifications, no matter how they were created, resulted in *mirror-image* waveforms in FC and R.

A brief stimulus to MRF evoked mirror-image responses in FC and R that had the same polarities as and similar waveforms to those evoked by conditioning, but in this case the *mechanism of regulation* of evoked waveforms was found to be different. The configuration of conditioned waveforms (i.e., peak latency, amplitude, duration) was determined by parameters of the stimulus situation, whereas waveforms evoked by MRF stimulation were uniformly large in amplitude and long in duration (20 to 30 sec). Novel stimuli or strong cutaneous shocks also evoked similar 20- to 30-sec tonic responses in both FC and R, a finding which suggests that these stimuli, like the

MRF pulse, all belong to the same class of stimuli and are perhaps mediated by the same cerebral mechanism.

Bilaterial cryogenic (Skinner 1971c) ITP blockade was found by Skinner and Yingling (1976) to abolish the ability of the *conditioned* tone to evoke responses in R or FC. Under these conditions, however, MRF stimuli could still produce a response in R, a finding which suggests that the *conditioned response in R is not mediated by MRF activation*. Whether or not the conditioned R response is dependent upon a conditioned FC response is difficult to determine. ITP blockade invariably interrupts thalamocortical inputs to FC as well as FC-R projections. In order to prove that conditioned R responses are dependent upon FC responses, the latter would have to be evoked by some as-yet-unknown means during ITP blockade of FC-R fibers alone. Since the physiological and anatomical evidence of Steriade and Wyzinski (1972), Yingling and Skinner (1975), and Scheibel and Scheibel (1966, 1967a) convincingly supports a direct FC-R projection, conditioned slow potentials in R are probably dependent upon the occurrence of FC responses.

Distinctions Among SPs

Novelty or conditioned significance inherent in a given physical stimulus will result in SPs that can appear quite similar to each other. These two responses, though, are mediated by separate mechanisms. For example, responses in R to novel stimuli are not abolished following ITP blockade, whereas those elicited by conditioned stimuli are (Skinner and Yingling 1975). This result clearly distinguishes between the two responses even though the waveforms and polarities may be identical. Identifying the underlying neural mechanism may, therefore, be necessary to distinguish among some types of SP responses.

Loveless and Sanford (1974) showed that the human CNV is divisible into two components related to conceptually distinct cerebral processes: An early component that appears just after the warning signal was attributed to an orienting reaction (O-wave); and a late component that manifests itself just before the second stimulus was attributed to expectancy (E-wave). Similar independent modulation of these two components has been demonstrated recently in humans (Rohrbough et al., 1976) and in animals (Skinner and Yingling 1977, Skinner, in preparation). By averaging small blocks of 15 trials each, the latter investigators were able to study the development of frontal cortex SPs in the cat during acquisition of tone-shock conditioning. After overconditioning (500 to 1000 trials), the early negative SP component that usually follows the warning tone drops out and leaves unaffected the ramp potential that just precedes the cutaneous shock. This habituation of the early component is also seen in records in which the interstimulus interval is reduced from 4.0 to 1.2 sec, a situation in which the rise times of the SP components are forced to accelerate (Skinner 1971b).

Bilateral cryogenic ITP blockade abolished both the early and late CNV components in FC and R (Skinner 1971b, Skinner and Yingling 1977). This finding suggests that neither of the conditioned responses in R is entirely dependent upon MRF activation since stimulation of this latter structure during ITP blockade could still produce an SP in R (Skinner and Yingling 1976). A positive shift in the baseline occurs in R during ITP blockade, however, and this potential could reflect a constant process represented by one of the two positive CNV components. In support of this position, Luria and Homskaya (1970) have attributed the behavioral deficit following frontal lobotomy in man to perpetual orienting reactions that can no longer be terminated or brought under control by some process that has been lost. Thus, the positive baseline shift in R pursuant to ITP blockade may represent a constant orienting process (O wave) that can no longer be brought under control by inputs from FC. FC input to R may normally give rise to the expectancy process (E wave) that always follows the orienting reaction and perhaps suppresses it.

The Generators of Cortical SPs

Cyclic nucleotides have been implicated in the mediation of slow postsynaptic potentials in sympathetic ganglia (McAfee and Greengard 1972, Greengard and Kebabian 1974, Weight et al. 1974, Libet et al. 1975, Kebabian et al. 1975). Once evoked, these intracellular potentials persist for many seconds. The pharmacology of the specific transmitters involved (Libet 1970, Greengard and Kebabian 1974), the intracellular dynamics of the specific cyclic nucleotides activated (Greengard and Kebabian 1974), and the resultant ionic effects that produce the post-synaptic membrane potentials (Weight and Votava 1970, Weight and Padjen 1973, Siggins et al. 1973, Schulman and Weight 1976) have been studied in the sympathetic ganglion model. Tonic increases or decreases in firing rates of neurons following local iontophoretic application of various neurotransmitters and cyclic nucleotides suggests that similar slow excitatory and inhibitory mechanisms exist in the cerebral cortex (Stone et al. 1975, Phillis et al. 1975). Subcortical effects have also been noted; local application of acetylcholine in R will silence spontaneous firing of units in this structure for many seconds (Ben-Ari et al. 1975). Thus, cerebral slow potentials associated with higher cognitive functions may have generators that are related to the mechanism of membrane potential changes observed in neurons of the sympathetic ganglia.

Evidence from Skinner et al. (1978b), based on a new cryogenic method of neurochemical fixation in the conscious rat, showed that a close correlation exists between shifts of cortical slow potential amplitude and cyclic AMP (3', 5'-adenosine monophosphate) level that follow cutaneous electric shock. Another rat study (Skinner et al. 1978a) showed that several types of psychologic and physical stress result in a reduction of cyclic AMP level compared to that of unstressed controls. The effects of cutaneous stimuli (25 V, 150 Hz, 0.5-sec duration) caused an immediate increase in cyclic AMP in parietal cortex that then decreased over a 30-sec interval in parallel with the development of a positive SP recorded from the same region ($r = 0.77$, $P \leq .01$). Only SPs recorded from the same small region of parietal cortex in which the chemical measurements were made correlated with the cyclic AMP content, a result which suggests that generators of the SP and cyclic AMP shifts are confined to the same region. Positive SPs evoked by the shock did not reverse in polarity across the cortex, from surface to depth, a finding which suggests that the SPs are generated by a closed-field dipole.

Cyclic nucleotides are thought to be intracellular mediators between the neurotransmitter arriving at the postsynaptic membrane and the regulation of ionic gates in the membrane that determines the cellular response to the neurotransmitter (Greengard and Kebabian 1974). Since direct extracellular application of cyclic AMP to cortical neurons by a micropipette causes them to stop firing for several seconds (Stone et al. 1975, Phillis et al. 1975), the phasic increase followed by tonic reduction of cyclic AMP described above suggests that cutaneous shock activates first a rapid inhibitory input to parietal cortex neurons that then becomes tonically disinhibited over a period of 30 sec to drop below the control level. This evidence is not conclusive because it is not known upon which cells the injected cyclic AMP operates or in which cortical cells the cyclic AMP increases following shock. All that can be concluded is that a surface positive SP in the parietal cortex is correlated with a decrease in cyclic AMP in underlying tissue.

The coupling between SPs and underlying neuronal activities is not very precise. This has been explained in part by the diffusion time required for potassium ions to move between neurons and nearby glial cells whose interconnected syncytium actually produces the SPs (see Somjen, this volume). The slow membrane potentials in the sympathetic ganglion nerve cells seem to be produced by reduction in the leakage currents of sodium and potassium ions (Weight and Votava 1970, Weight and Padjen 1973), a finding that implies modulation of the length constant of membranes much like that produced by myelin on an axon. Thus, a slow IPSP in these cells resulting from decreased sodium conductance could have the net effect of making some remote synaptic EPSPs more effective in their influence on a trigger zone in the cell and thereby could increase the firing rate even though the cell is hyperpolarized.

In a fairly uniform structure like the thalamic reticular nucleus, however, there does seem to be a fairly close correspondence between the duration and polarity of evoked SPs and the firing of neurons, as illustrated in Fig. 1 and 2. In Fig. 1B a negative SP is seen to follow each 8-c/sec impulse to the medial thalamus (ncm) and to recruit in amplitude; this phasic slow potential (best seen after the last pulse in the stimulus train, arrow) only lasts 100 msec. Fig. 1C shows that this same thalamic train of stimuli recruits excitation of R units for approximately the same interval as the negative slow potential. Fig. 2B shows a slow positive potential in R elicited by a brief stimulus to MRF that persists for many seconds. This same stimulus to MRF also silences spontaneous units

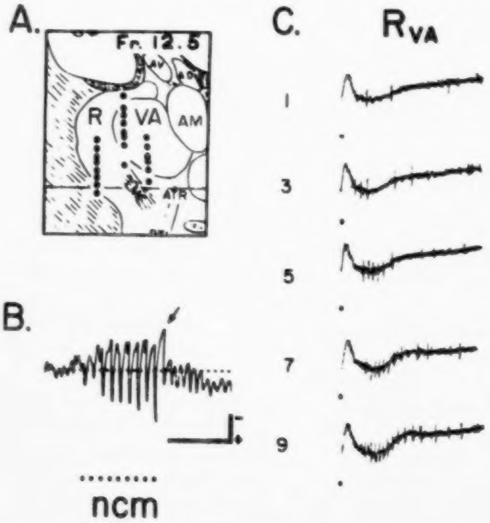

Fig. 1. Slow potentials and unit activity evoked in nucleus reticularis thalami by medial thalamic stimulation. A. Filled circles: Location of units encountered in the anterior portion of nucleus reticularis thalami (R) adjacent to nucleus ventralis anterior (VA) that were responsive to 8 c/sec stimulation of nucleus centralis medialis (ncm). Open circles: Units that were not responsive to ncm stimulation. B. Phasic slow potentials recorded in the same region of R_{VA} by a DC amplifier during ncm stimulation; negative responses occur in the interval between the positive-polarity recruiting responses and are best seen following the last stimulus in the train (arrow); calibrations 200 µV, 1 sec. C. Oscilloscope traces of units in R_{VA} responding to the first through the ninth impulse of an 8 c/sec stimulus train to ncm; the trace length is 100 msec following each stimulus pulse. (Adapted from Yingling and Skinner 1975 and Skinner and Yingling 1976.)

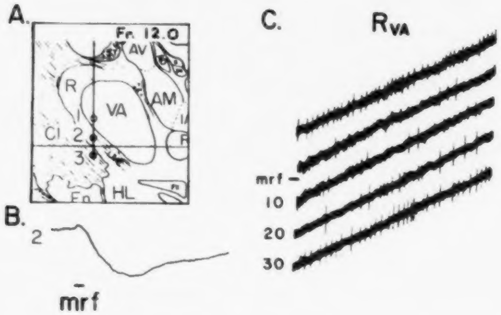

Fig. 2. Slow potentials and unit activity evoked in nucleus reticularis thalami by mesencephalic reticular stimulation. A. Filled circle: Location of recording electrode in the anterior portion of nucleus reticularis thalami (R) adjacent to nucleus ventralis anterior (VA) that showed a slow-potential response to a brief stimulus (2-6 V, 150 c/sec; 0.5 msec duration, 30 msec train) to the mesencephalic reticular formation (MRF). Unfilled circles: Location of electrode that showed no responses to same MRF stimulation. B. Tonic slow potential of positive polarity recorded in R_{VA} *following a brief stimulus to MRF; trace length is approximately 1 min, and peak amplitude is 12 mV. C. Oscilloscope traces of spontaneously firing* R_{VA} *units that are inhibited by a brief stimulus to MRF; each trace length is 1 sec and shows activity immediately before and after MRF stimulus and 10, 20, and 30 sec later. (Adapted from Yingling and Skinner 1975 and Skinner and Yingling 1976).*

in R for approximately the same interval of time as concurrent slow potentials, a result illustrated in Fig. 2C. Note by comparing Fig. 2B and 2C that the unit response latency is rapid, whereas the onset latency of the slow potential is on the order of a second; furthermore, the peak inhibitory effect on unit activity is earlier (i.e., immediate) than the peak of the slow potential shift (approximately 15 sec).

In conclusion, it appears that slow extracellular negative shifts are associated with unit excitation, and extracellular positive responses are related to unit inhibition, at least in R. Whether this same relationship holds for unit activities and slow potentials in other parts of the brain is not known, although some evidence indicates that multiple unit activity increases in the lateral geniculate are associated with negative extracellular slow potentials (Rebert 1973). This general relationship does not seem to hold for parietal cortex in which positive SPs are associated with a reduction in cyclic AMP, a putative mediator of cellular inhibition. The cortex, however, contains numerous types of cells, and the pattern of interactions that give rise to cortical SPs may be quite complex. The electrogenesis of cerebral slow potentials associated with higher cognitive processes is still uncertain, but accumulating evidence points toward a chain of events in which cyclic nucleotides regulate slow postsynaptic potentials in neurons that in turn modulate extracellular K^+ concentrations which effect responses in the surrounding glial cell syncytium to produce the recorded closed-field potentials.

Sensory Evoked Potentials: Selective vs. General Regulation of Relay Nuclei

Regulation of Cortical Evoked Potentials by MRF and FC

Selective attention in human subjects results in enhancement of cortical evoked responses to attended stimuli (Spong et al. 1965, Hillyard et al. 1973, Hillyard and Picton, this volume), whereas arousal causes the enhancement of responses to relevant and irrelevant stimuli alike (Näätänen 1970). In animals, MRF stimulation causes enhancement of evoked responses in all sense modalities independently of the precise location of the stimulating electrode in the structure (Bremer and Stoupel 1959, Dumont and Dell 1960). These findings suggest that regulation of evoked potentials by the MRF is *nonspecific,* as in the process of general arousal. In contrast, the MT-FC-R system regulates sensory processes selectively. For example, various sense modalities affected by intervention in the ITP depends upon the precise location of the blockade. Cryoprobes placed bilaterally in a certain part of the ITP will enhance visual but not auditory evoked potentials when cooled to 15°C and will enhance both when cooled to 10°C (Skinner and Lindsley 1971). Alexander et al. (1976) showed that FC stimulation with a matrix of electrodes inhibited spontaneous and driven single units throughout auditory cortex; the particular units inhibited, however, were specific to the point in FC stimulated. These results suggest that regulation of evoked responses by the MT-FC-R system is *specific* and may be involved in the process of selective attention.

Regulation of Sensory Evoked Responses by R

Both ITP blockade and MRF stimulation appear to enhance cortical evoked potentials by facilitating transmission through thalamic relay nuclei (Skinner and Lindsley 1971, Rapasardi et al. 1974, Bartlett and Doty 1974). This opening of thalamic gates may be effected by two separate mechanisms, which block the tonic inhibition exerted by R on thalamic relays. As evidence, stimulation of R is found to inhibit transmission of sensory information through thalamic relay nuclei (Skinner and Yingling 1976, Yingling and Skinner 1976), a finding which demonstrates that R is the source of a powerful inhibitory influence (Fig. 3). Evidence that R maintains a tonic output is seen in records where R units fire continuously (Fig. 2C).

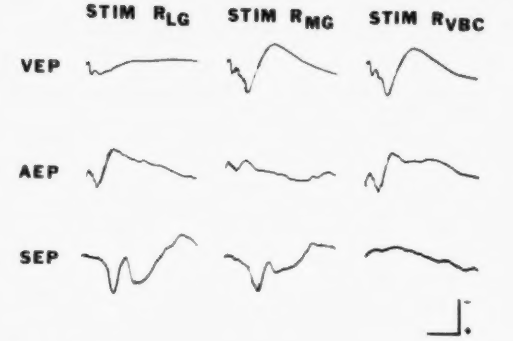

Fig. 3. Inhibition of evoked potentials in three major sense modalities by stimulation of various regions of nucleus reticularis thalami (R) adjacent to different thalamic relay nuclei: lateral geniculate (LG), medial geniculate (MG), and ventrobasal complex (VBC). Visual evoked potentials (VEPs) were elicited by optic-tract stimulation and recorded in primary visual cortex. Auditory evoked potentials (AEPs) were elicited by stimulation of the brachium of the inferior colliculus and recorded in primary auditory cortex. Somatosensory evoked potentials (SEPs) were elicited by stimulation of stainless steel wires sutured through the skin of the hind leg and recorded in the contralateral somatosensory cortex (far lateral anterior sigmoid gyrus). Conditioning stimuli of 250 c/sec, 20 msec trains were delivered to either R_{LG}, R_{MG}, or R_{VBC} 50 msec prior to the test stimulus. Stimulation 1 mm on either side of these various regions of R had no effect on reducing the primary sensory evoked potentials. Calibrations: 200 μV; 4 msec (VEPs), 10 msec (AEPs and SEPs). (Adapted from Yingling and Skinner 1976).

These spontaneous units can be inhibited by MRF stimulation and their ability to be driven to higher rates by the MT-FC-R system can be interrupted by ITP blockade. Thus, *disinhibition of thalamic relay nuclei could be effected by either reduced excitation from FC to R or by increased inhibition from MRF on R.*

Selectivity of the MT-FC system in the regulation of sensory evoked potentials implies that FC projections through R to sensory channels maintain modality-specific connections. Specificity of inhibitory projections of R into thalamic relay nuclei has been demonstrated by Yingling and Skinner (1976), who found that stimulation of the portion of R adjacent to a given thalamic relay nucleus inhibited transmission *selectively* in this afferent pathway, without influencing other sensory channels (Fig. 3). Since MRF stimulation enhances evoked potentials *generally*, this structure must have widely distributed axonal projections to R cells. Fig. 4 illustrates these specific and nonspecific projections of FC and MRF systems to R cells, a feature of central importance in the neurophysiological model discussed below.

Theoretical Model for Regulation of Sensory Input to Cerebral Cortex

Physiological and anatomical data have been presented to support the schema (shown in Fig. 4) by which sensory inputs to cerebral cortex are regulated. FC is shown to have phasic excitatory (Ep) influences on R cells that are specific in their projection. In contrast, MRF has tonic inhibitory (I_T) control over R neurons via diffuse or nonspecific connections. R cells project to specific thalamic relay nuclei (Th Relay) and form a parallel series of inhibitory gates that control the transmission of afferent activity. The pattern of activity in R that results from its dual regulation by FC and MRF determines the pattern of input from sensory receptors that reaches respective primary projection cortices (PC). Inputs to FC and MRF are not specified by the model because of insufficient data. Both structures, however, receive information from external and visceral receptors via connections with other regions of the brain (not shown in the diagram) including the limbic and autonomic nervous systems.

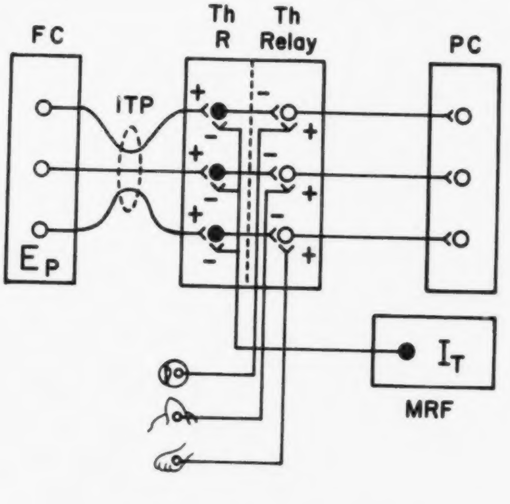

Fig. 4. Neurophysiological model for the regulation of sensory input to cerebral cortex. FC = frontal cortex; ITP = inferior thalamic peduncle; Th R = thalamic reticular nucleus; Th Relay = thalamic relay nuclei for visual, auditory, and somatic afferent channels; PC = primary projection cortex; MRF = mesencephalic reticular formation. White neurons are excitatory and black ones inhibitory. FC neurons produce phasic excitation (E_P) of R cells via specific projections. MRF cells produce tonic inhibition (I_T) of R cells and have nonspecific, widely distributed projections.

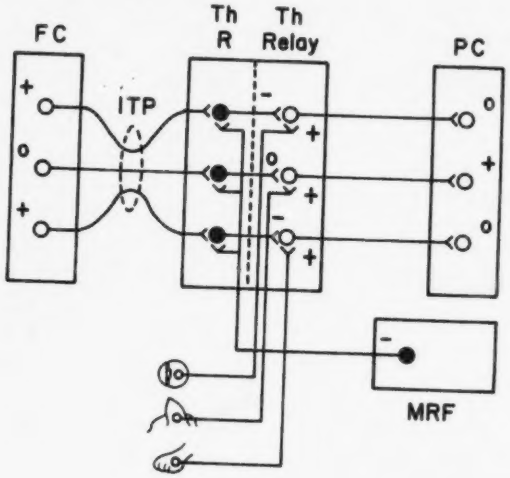

Fig. 5. Example in which the neurophysiological model selects auditory input to the cerebral cortex because of a particular pattern of activity in FC and MRF. + = synaptic excitation of cell; – = synaptic inhibition of cell; 0 = no excitation or inhibition. Abbreviations same as Fig. 4.

An example of a particular state of the model is shown in Fig. 5, which illustrates how a pattern of activity in FC could result in the selective transmission of input to the auditory cortex, as in selective focusing of attention to sound stimuli. The connections in this model imply that *selective suppression of irrelevant stimuli* is exerted by the pattern of activity in FC; that is, FC must have information as to what channels to close. This contention is supported by observation that ITP blockade enhances irrelevant evoked responses (Skinner and Lindsley 1967). The role of FC in suppressing interfering stimulus events in the brain has been suggested more recently by Bartus and Levere (1977) who showed that the behavior of monkeys with dorsolateral frontal ablations was guided by irrelevant as well as relevant stimuli in a discrimination task in which both types of cues were presented sequentially.

A pattern of activity in R may begin to form initially from a condition in which all gates are opened by a strong stimulus to MRF. As MRF output declines, relinquishing priority of inhibitory control over R cells, selective excitation of R cells by FC may occur and thus close thalamic gates, one-by-one, until only the attended channel remains open. This sequence of events in which orienting reactions are replaced by expectancy or selective attentiveness is, perhaps, reflected in the sequential O-wave and E-wave components of SPs in R and FC that occur during the CNV and related paradigms. Another strong or novel stimulus could activate the MRF and cause it to exert generalized priority control over R units and reopen the selectively closed gates. If MRF excitation is not intense enough to drive all the gates open, it may simply drive the pattern in R that is being sculptured by the FC into a *less selective* prior condition. It is important to realize that it is the joint regulation of R by FC and MRF that gives rise to the pattern of input to cerebral cortex. These two systems appear to vie constantly for control over R cells, thus titrating the processes of general arousal against selective attention.

For example, King and Skinner (1975) have shown that mild 8-c/sec MT stimulation will disrupt single alternation behavior, as will partial ITP blockade. In both cases the descending pattern of activity from FC to R is changed, perhaps resulting in the inability of an animal to control its sensory channels in a way that is necessary to perform the task. In the case of mild MT stimulation, the animal's performance deficit can be reversed by MRF stimulation. This deficit reversal is not the case for partial ITP blockade, however, for in this case the pattern from FC to R is lost, not merely superimposed upon a generalized bias that can be neutralized by another of opposite sign.

This model does not pretend to solve the mystery concerning the nature of the behavioral deficit that occurs following frontal lobotomy, although it suggests explanations for some observations. For example, Konorski and Lawicka (1964) observed that frontal preparations were easily distracted by irrelevant stimuli that impaired performance. The present model predicts that without selective FC excitation of R, irrelevant sensory gates would remain open, and thus allow non-pertinent information to ascend continuously to the cortex. This cortical excitation by irrelevant stimuli may underlie the hyperdistractibility characteristic of frontal animals and lobotomized patients.

A major question remains unanswered: "How does the pattern of activity in FC develop to set selectively the gates in R that determine the pattern of sensory input to the cerebral cortex?" A definitive answer remains as a challenge to the future expansion of this model, although some clues are presently available regarding transactions in FC. Imbert et al. (1966) have shown in "cortical shell" cat preparations that FC receives cortico-cortical inputs from virtually all primary and association cortices. Such a configuration allows for, but does not prove, reiterative regulation of FC: FC-R-thalamic relays-primary cortex-FC. Such reiterative thalamocortical circuits have always been presumed to underlie EEG synchronous activities. As stated earlier, the inherent resonant periodicity of recruiting responses seems to depend on a delay in the cortical component of the underlying circuit. Whatever is the source of this delay (e.g., dendritic propagation, lateral inhibition, slow PSPs), FC recruiting responses appear to have open-field dipoles with reversal potentials (Spencer and Brookhart 1961). SPs in FC, however, do not appear to have the same type of dipole generators. Kelly et al. (1969) and Arezzo et al. (1975) have shown that FC potentials in the monkey evoked by irrelevant sensory stimuli have closed-field dipoles (i.e., no reversal potentials), a finding which suggests important bioelectric processes in FC that are distinct from those associated with recruiting responses. This list of FC transactions certainly must continue with the work in animals by Rowland, Fuster, Stamm, and Marczynski (all in this volume), but the incorporation of their data into the present model is not yet tenable. Neither is the analytic work in parietal cortex by Mountcastle (1976) whose experiments are also designed to backtrack from attentive behavior into the underlying neocortical mechanisms. Further investigations into molecular mechanisms responsible for slow-potential FC shifts that are correlated with attentive behavior will undoubtedly be the most important source of new information to be incorporated into the thalamic gating model.

The present model attributes a selective pattern of activity to FC and a level of activation to MRF and shows how these posited activities *jointly regulate* inhibitory gates in R that control the ascent of sensory information through the thalamus to the cortex. The power of this model lies in its ability to explain changes in three types of bioelectric activity traditionally associated with the processes of arousal and attention in both animals and humans. EEG synchronization in FC may be an activity associated only with an idling state in the thalamic gating system, but its use as an investigatory probe, especially in the form of recruiting responses, has been helpful in determining some of the physiological features of the gating mechanism. Any theoretical model of attention must deal effectively with this phenomenon, even if synchronous activities *per se* are shown to be of no particular importance. SPs recorded in the gating system have confirmed the dual regulation of R seen with the recruiting response probe. Frontal cortex SPs appear to depend upon the integrity of a subcortical system that is projected centripetally via ITP. This projection, however, may not be the only source of input that sculptures the SP pattern of activity in FC, for the frontal lobe is the recipient of massive cortico-cortical projections from all parts of the cerebral mantle. The MRF is commonly associated with the processes of orienting and arousal, and its impact upon the thalamic gating system at R may eventually explain how both orienting (O-wave) and expectancy (E-wave) components can appear in cortical SPs as demonstrated by Loveless and associates (this volume). Finally, the thalamic gating model offers a ready explanation for the regulation of sensory evoked responses by both specific and nonspecific mechanisms. Hillyard and Picton (this volume) have identified in the human cortex an N100 component of the sensory evoked response that seems to be related to "stimulus-set" or stimulus-source selection and a P300 component related to "response-set" or stimulus relevance selection. *The present neurophysiological model suggests a theory of attention in which selection occurs via active suppression of irrelevant stimuli controlled jointly by FC and MRF interactions on the inhibitory gates in R.* These interactions determine not only what gates are closed (source selection), but how intensely they are closed by the titration of the two systems (relevance selection). These regulatory features of the neurophysiological model developed with animal experiments appear to provide the basis for explanation of the independent modulation of the N100 and P300 evoked potential components as well as the O-wave and E-wave components of slow potentials, and therefore provide a unifying theoretical framework to explain several event related potentials in the human brain.

Comments on the Skinner Model

Hillyard expressed the view that, at present, evidence from human ERP studies of attention and animal physiological studies of the kind presented were so far apart that no definite conclusions could be reached as to whether a particular model, such as Skinner's, was right or wrong. He welcomed it, however, as providing a creative framework that suggested experiments to be undertaken. These could well give direction to hitherto independent lines of investigation in a way that would bring them closer together.

One experiment suggested by the model would involve showing that the *nucleus reticularis thalami* physiologically has the capability to select or to gate information in a situation parallel to one in which human psychological experimentation has shown that good selective attention occurs - i.e., a situation where stimuli are presented from different sources, at a rapid rate, and with a very high information load. One could, for example, record from two subdivisions of R, which control different selective sensory systems, in circumstances where the animal was required to attend first to one source and then another. Only then could one determine whether the animal is actually behaving as the model predicts.

The model also suggests other links with human data. For instance, it suggests a place in frontal granular cortex that might be susceptible to disruption in patients suffering from stroke or other forms of cerebral damage in the appropriate area. Such patients, with the equivalent of an inferior thalamic peduncle lesion, could be investigated for their ability to regulate inputs.

Unfortunately, human evoked potential data do not yet provide evidence for the modulation of primary cortical responses in a form that would support Skinner's model. Potential changes can be recorded from the primary cortex when a person is attending to stimuli, at least in the somatosensory mode, and possibly in the auditory mode; however, these primary potentials do not seem to show systematic changes related to attention.

Zappoli thought that the Skinner model, based primarily on data from experiments with cats, was not entirely supported by existing evidence from man. Skinner's findings show that the mediothalamic-frontocortical system may play an important role in generating and regulating anterior frontal surface negative SPs; however, Zappoli et al. (this volume) have observed CNVs in bilateral prefrontal lobotomized patients in whom thalamo-frontal pathways have been severed by the technique of Freeman and Watts (1947, 1966). Regeneration must be considered impossible in such cases since autopsies have always shown extensive retrograde degeneration of the thalamic dorsomedial nuclei. Furthermore, the absence of degeneration of reticular and intralaminar nuclei suggests that the dorsomedial-thalamofrontal system is not indispensable to CNV development over the frontal region in humans, as the model implies.

These findings, together with those of Gazzaniga and Hillyard (1974) on CNVs in "split-brain" patients, and of Marsh and Thompson (1973) and Weinberg and Papakostopoulos (1975) on the bilateral symmetry of the CNVs activated in different right-left tasks, suggest that classic CNV activity is a diffuse electrical event essentially related to a unitary, general physiological brain process (e.g., arousal) presumably mediated by the non-specific ascending reticular system. The differences in morphology and polarity of CNVs detectable in different brain structures are probably related above all to their intrinsic anatomo-functional characteristics and to the method commonly utilized in recording these potentials.

Zappoli pointed out that the anomalies between Skinner's animal data and his human data were by no means unique and served to emphasize the caution that should be exercised when extrapolating from animal to man.

Skinner replied that on the whole Dr. Zappoli's data supported rather than refuted his model. One of the outstanding questions is how the frontal cortex receives its program in order to produce the gain. It certainly receives inputs from various subcortical regions and other cortical areas. Evidence (Imbert et al. 1966) from "cortical shell" preparations in which only the cortex, white matter, and its circulation are left intact, suggests that frontal granular cortex is the home of the cerebral map. Stimulating every part of the cortex and recording from every part of the cortex reveals that practically everything leads to the frontal cortex, including, via cortical-cortical pathways, all association and primary receiving areas.

In man the inferior thalamic peduncle travels in the medial ventral quandrant of the forebrain, a region normally regarded as unsafe for surgical intervention. Therefore, Skinner considered it unlikely that transections in Zappoli's patients would have impinged upon the ITP. Skinner also argued that the observation of CNV in prefrontal lobotomized patients was not entirely inconsistent with his model. If lesions in thalamocortical pathways in these patients were extensive enough to rule out this source of input, then the presence of CNVs strengthens the suggestion that frontal cortex receives its program via cortico-cortical pathways.

Skinner replied that on the whole Dr. Zappoli's data tended to expand rather than contradict his neurophysiological model. One of the outstanding questions is how the frontal cortex receives its signal to produce a slow potential. This region receives axons from both the thalamus and the *cortex*. Physiological evidence (Imbert et al. 1966) from cortical shell preparations in which only the cortex, white matter and circulation are left intact, suggests that the frontal cortex is the "Rome" of the cerebral mantle to which "all roads lead." That is, the sensory and association cortices all project, unidirectionally, to the frontal lobe. If lesions in thalamocortical pathways were extensive enough in Dr. Zappoli's patients to rule out the subcortical source, then the continued presence of the CNV's strengthens the suggestion that the frontal cortex receives its SP-evoking input via cortico-cortical projections. Perhaps, Skinner said, an arrow should be drawn from the projection cortices (PC) in Fig. 4 to the frontal cortex (FC), but this action must await experimental observation in animals in whom the surgical disruptions can be completely controlled.

Degeneration in medialis dorsalis thalami does not indicate extensive frontal granular cortex denervation. The entire medial thalamic nuclear complex systematically projects to the frontal lobes (Kievit and Kuypers 1977). Partial blockade in the inferior thalamic peduncle or the frontal granular cortex only partially reduces the amplitude of cortical or thalamic recruiting responses and only partially degrades behavioral performance (Skinner and Lindsley 1967). In man the ITP travels in the medial ventral quadrant of the forebrain, a region normally regarded as unsafe for surgical intervention. Therefore Skinner considered it unlikely that transsections in Zappoli's patients would have impinged upon the ITP where the "bottleneck" of fibers are bundled together.

A PARSIMONIUS MODEL OF MAMMALIAN BRAIN AND EVENT RELATED SLOW POTENTIALS[1]

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During the past 15 years new ideas have been formulated concerning the basic principles that govern the functioning of self-organizing systems (von Foerster 1960, MacKay 1965, Uttley 1976) and the mode by which the information may be transmitted (Marczynski 1976, Brudno and Marczynski 1977). Models of mammalian brain have been presented before (John 1967, Smythies and Adey 1970, Kornhuber 1973, Pribram and McGuinnes 1975, Marczynski and Burns 1976), and many aspects of the model presented here incorporate previous ideas, particularly those of Kubie (1953), MacKay (1965), and MacLean (1970). The author realizes that the model may be repudiated by some investigators as an oversimplification; however, despite its parsimonious character, this model pulls together a wide spectrum of experimental and clinical data, including those on event-related slow potentials (ERSPs) and their pathognomonic significance. Hence, the oversimplifications may perhaps be redeemed by the potential heuristic value of the model.

Fig. 1 illustrates a simple feedback control loop proposed by MacKay (1965). Note that hypothetical substrates responsible for generating the *indication of goal* (I_G) project to a *matching* or *comparator* (C) system. In order to function, C must receive feedback in the form of sensory input generated by the organism during interaction with the environment in the *field of action*. The brain must also contain substrates that can be labelled as *selector* whose main function is to determine the general mode of motor response by influencing the *effector*, i.e., all substrates responsible for execution of movements. The *effector* thus represents the motor repertoire of the organism.

Fig. 2 illustrates a more elaborate model of information flow in the mammalian brain. This model, based on the theoretical servo-loop shown in Fig. 1, differs from the MacKay model in several crucial ways. First, anatomical and physiological details of well-known pathways and local neuronal circuits have been added to the cybernetic framework of MacKay. Second, the mammalian model includes two distinct feedback loops, whereas the cybernetic model proposed only one which does not reflect the dichotomy or "schizophysiology", as MacLean put it, of the manner in which sensory input is processed in the mammalian brain. The model we propose (see also Marczynski and Burns 1976) is consistent both with the basic functional anatomy of the mammalian brain and with the cybernetic model of Uttley (1976), who used a computer model of two qualitatively different pathways impinging on the same substrate to provide mathematical and experimental evidence for the rationale and advantage of such an arrangement. Despite the mushrooming of the association thalamo-cortical system and the cortico-cortical pathways in higher mammals and man, the phylogenetically older medial forebrain bundle (MFB) continues to perform a vital function in conveying septal feedback to the limbic system. Moreover, the *selector* is differentiated into two basic components: one selecting a general mode of motor response and the other labelled as the *ascending reticular activating system* (ARAS), which carries two functionally different projections: a cholinergic and a catecholaminergic. Finally, at the thalamic and cortical level the basic recurrent inhibitory circuits have been included; they are responsible for the phasing of neuronal activity into the alpha-like EEG patterns associated with hyperpolarization of large populations of neurons in the thalamus and cortex (cf. Andersen and Andersson 1968).

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[1] *Ed. Note:* This model originally constituted the concluding section of the paper by Dr. Marczynski on 'Neurochemical mechanisms in SP genesis: a summary' which is included elsewhere in this volume. Because of its direct relevance to the topic of Neurophysiological Models it has for convenience been incorporated at this point, but should be read in conjunction with the full paper.

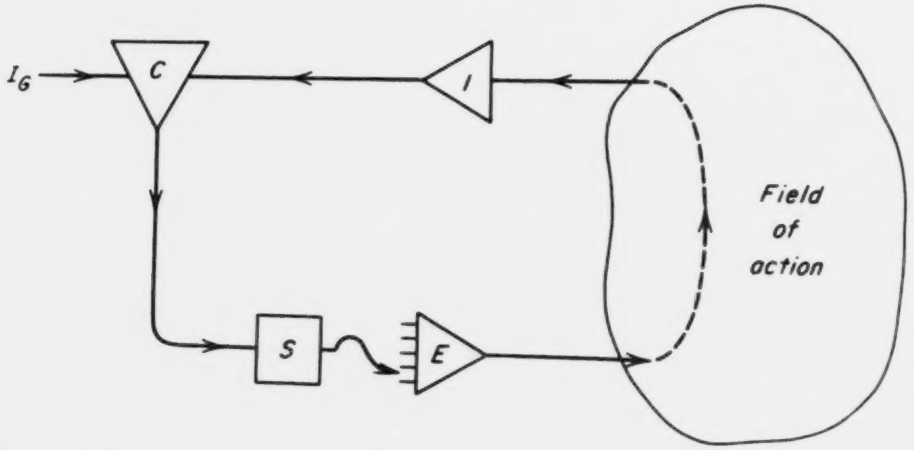

Fig. 1. Simple feedback control loop of MacKay (1965), depicting the flow of information responsible for adaptive behavior. Components include an indication of goal (I_G), comparator (C) or evaluator of the status of the system resulting from selection (S) of a particular response from the effector (E) repertoire, and an indicator (I) of the quality of the process under control (e.g., temperature).

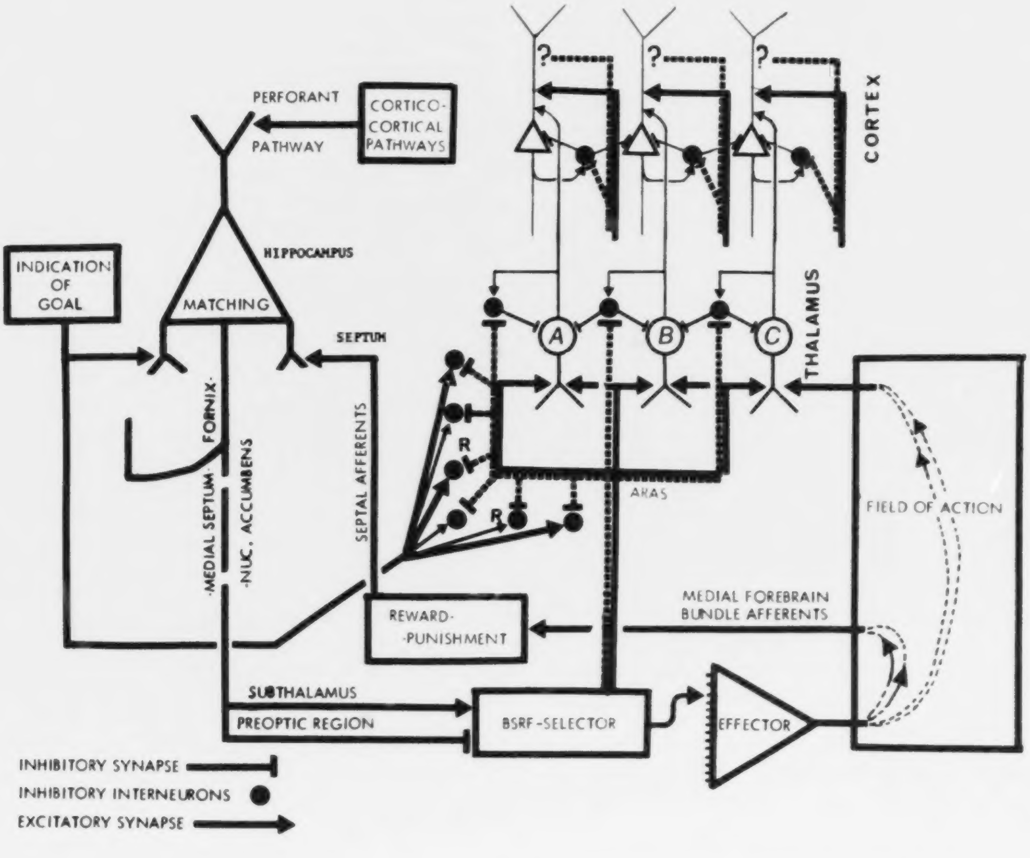

Fig. 2. Model of information flow and processing of sensory input in the mammalian brain. See text for details.

Hippocampal main input-output relationships

The basic "wiring" of the limbic system is represented by a CA1 pyramidal cell of the hippocampus (*matching*), whose synaptic organization is relatively well established (MacLean 1970 and Gloor et al. 1964). The single cell receives two different inputs: one is transmitted from adjacent entorhinal cortex via perforant pathways of Cajal to apical dendrites of the cell, and the other comes from the MFB via the septal pathways and impinges on basal dendrites or proximal sections of apical dendrites. Since septal input is much closer to the soma than is cortical input, septal input is much more influential than perforant input in modulating *comparator* function (cf. MacLean 1970). It should be noted that the corticofugal pathways can reach the hippocampus either monosynaptically, as shown in Fig. 2, or via three synapses: dentate cell dendrites, CA3 dendrites, and Schaeffer collaterals (Smythies and Adey 1970), which are not shown for simplicity.

Typical responses to a volley of impulses in the afferent perforant path are excitatory postsynaptic potentials (EPSPs) in the apical dendrites. The resulting weak depolarization is insufficient, in most instances, to fire the cell. The cell membrane, however, is biased, and the threshold may be reduced so that the cell can be more readily fired by input from the septum. Such a coincidence of two excitatory inputs on the same cell may serve as a conditioning mechanism in which the effect of weak input from the entorhinal cortex depends upon input from the septum (cf. Gergen and MacLean 1964).

Thalamocortical feedback

During a successful or unsuccessful interaction with the environment, sensory input, both proprioceptive and exteroceptive (including that from the cerebellum, channeled via the *brachium conjunctivum*) is projected to specific thalamocortical regions where the precise physical, spatial, and temporal characteristics of each modality are analyzed. Subsequently, the modalities converge and interact in numerous association areas of the thalamus and cortex. Thus, for instance, the distance from subject's hand to the perceived object is evaluated not only by "purely" visual characteristics, but also in terms of muscle effort that might be necessary to reach and lift the object (cf. Eccles 1966). It is apparent that these synthetic judgments, in most instances not realized by the subject, are based on previous somesthetic and kinesthetic experience, and they can be stored and retrieved as learned "praxias" (cf. Kornhuber 1971). The importance of active movements in the development of visual perception was demonstrated long ago (Held and Hein 1953). Thus, the three-dimensional visual world always has strong somesthetic and kinesthetic components that must be considered in trying to understand the genesis and topographical distribution of Sps. Hence, it is not surprising that the CNV, P300, the large *Bereitschaftspotential* preceding the Premotor Positivity (PMP) of Deecke et al. (1973) followed by a much deeper and long-lasting positivity, as well as the Skilled Performance Positivity of Papakostopoulos (this volume), and the positivity observed by Otto et al. (this volume) all occur over large areas of association cortex.

A more recent systematic study of the cortico-cortical pathways (van Hoesen et al. 1972) showed that each primary receiving cortex projects simultaneously to two topographically and functionally different association areas. For instance, visual information from striate cortex is projected to inferotemporal cortex and to the parietal association area. In the latter, visual information converges with similar projections from somesthetic and auditory cortex. In the infero-temporal cortex, visual information from striate cortex converges with fronto-orbital projections. Subsequently, integrated information is projected via two distinct pathways: one to fronto-orbital association cortex and the other to the ventral surface of the temporal lobe. The main feature of all cortical association areas is that their final projections converge on the ventral surface of the temporal lobe. The entorhinal cortex, which receives the final "version" of the information transforms resulting from polymodality interactions, projects via the perforant path of Cajal to hippocampal structures. It is therefore not surprising that even relatively small lesions involving the latter two links in cortical feedback to the limbic system may totally disrupt adaptive behavior in man, cause hallucinations involving all modalities, and sometimes produce a syndrome indistinguishable from schizophrenia (cf. Teuber 1972).

Medial forebrain bundle (MFB) feedback

MFB pathways and their numerous links with the *reward-punishment system* (cf. Olds 1964, Miller 1961) process and categorize sensory input in terms of the fulfilment of organism needs. These functions are evidenced by the fact that the rate of self-stimulation in these pathways and/or nuclei associated with them is closely related to primary drives. There are loci in which self-stimulation rate is related to food deprivation and inversely related to androgen level and sex drive. At another nearby locus, self-stimulation rate may covary with serum androgen level and with food deprivation, or it may only depend on androgen level (cf. Olds 1961, Brady 1961). However, the view that level of motivation is directly related to specific behavioral patterns or the sumtotal of individual drives would be a gross oversimplification. Even in lower mammals, the manner in which primary drives and *reward-punishment* substrates function shows that emotional states generated in pathways involving the hypothalamus, anterior thalamus, forebrain, and midbrain limbic system (e.g., Papez circuit) strongly influence the expression of primary drives. The latter are even further influenced by previous experience (cf. Sherer 1961).

The modulation of primary drives becomes gradually more apparent in higher mammals, particularly in primates and man (cf. Brutkowski 1965, Nauta 1971). In man the frontal association cortex and its reciprocal connections with other systems have all the attributes to function as the main modulator of the *indication of goal* (cf. Nauta 1971). Numerous clinical data strongly support this view (cf. Teuber 1972). In man the substrates that generate primary drives are modulated by organismic needs as well as by cultural tradition, ethical considerations, and philosophical concepts transmitted from one generation to another. Man is the only creature that can walk to the gallows with a smile to defend his beliefs. All these considerations provided the rationale for separating the *indication of goal* from MFB pathways in the proposed model.

More recently, the strategic position of frontal association cortex was further emphasized by electrophysiological confirmation of its commanding role in the regulation of the thalamic reticular nucleus (R), which can be best defined as a pool of inhibitory neurons responsible for gating sensory input at the specific thalamic nuclei (Skinner, this section). It appears almost certain that a specific spatio-temporal pattern of excitatory impulses from the frontal association cortex to R determines the scope of selective attention. Accordingly, despite the wide distribution of the CNV over frontal and postcentral areas, this potential should have modality-dependent components. Indeed, two components of the CNV with characteristic distributions have been observed during auditory and visual discrimination tasks (cf. Hillyard 1973).

Thalamocortical vs. medial forebrain bundle feedback

Thalamocortical input is extremely variable and is designed to provide an objective analysis and a faithful image of rapidly changing physical properties of environmental and proprioceptive stimuli. Within a fraction of a second, patterns of sensory input may dramatically change, and these changes are most likely reflected in transforms of information conveyed to the limbic system from the cortex via the perforant pathway of Cajal. In contrast, the traffic of impulses in MFB-septal feedback to hippocampal structures (and other limbic regions) is likely to reflect relatively slow changes in the functioning of centers reflecting bodily needs that are protected against dramatic swings by numerous homeostatic mechanisms designed to control the internal milieu and primary drives. The information content of the final output of this system impinging on the hippocampus and other limbic structures most likely changes over a time period of hours or even days. Hence, this homeostatically graded stream of information, which sculptures our personality and is ever present, may be compared to an *unconditional stimulus*, whereas the highly variable and brisk barrages of information impinging on the limbic system from the thalamocortical system may be compared to *conditional stimuli.*

Kubie (1953) was the first to suggest that duality of experience may be the basis of cognitive processes and even memory. MacLean (1970), after reviewing the unique synaptic organization of CA1 hippocampal pyramidal cells, claimed that the "union of internal and external experience is as important for memory as the combination of antigen and antibody in developing an enduring immunity". As already mentioned, mathematical analysis and computer studies of the pattern recognition capacity of units that simultaneously receive a stable and a variable input revealed the extraordinary power of such systems in categorizing the information in the variable input (Uttley 1976). A network of only 210 units, called informons, and 8400 "varying" channels could "learn" to recognize hand-printed numerals.

Hippocampal projections to the brain stem

The limbic descending pathways may excite or inhibit the brainstem reticular formation (BSRF) and ARAS (cf. Smythies and Adey 1970). The direction of these influences seems to depend on the outcome of the *matching* process in the hippocampus and other parts of the limbic system. The strongest arousal influences are generated when the organism is confronted with a novel barrage of sensory input. Upon repetitive presentation of such stimuli, and their classification and subsequent anticipation habituation occurs. After full habituation, signs of active suppression of the BSRF and ARAS, as evidenced by high-voltage, slow-wave EEG patterns (cf. Magoun 1964), are usually observed.

Relevant to our holistic view of brain organization is the morphology of single BSRF units described by the Scheibels (1967). BSRF units are characterized by profuse axonal ramifications, both ascending and descending, projecting to the thalamus, caudate nucleus, hypothalamus, as well as to the brain stem motor nuclei. A substantial portion of BSRF neurons project monosynaptically to the neocortex. In all these areas, each BSRF unit (including monoaminergic neurons) is likely to establish thousands of synaptic contacts. Since each unit has its own characteristic domain of influence, each neuron may be compared to a specialized module capable of activating and/or inhibiting uniquely a specific set of neurons in all aforementioned areas. All these attributes make the BSRF system the best choice for a *selector* of gross behavioral modes in our model.

During exploratory behavior and cognitive processes associated with selection of the most successful behavior in the *field of action*, limbic influences on the BSRF-*selector* seem to oscillate (cf. Smythies and Adey 1970). Such influences enable the organism to switch from one cognitive process and behavioral mode to another, thus introducing maximum flexibility and the elimination of unsuccessful behavior. Evidence for such a role of the descending limbic pathways in the maintenance of behavioral plasticity is abundant (cf. Smythies and Adey 1970, Pribram and McGuinnes 1975).

If the behavioral mode is successful, i.e., provides a match with the *indication of goal,* it is reinforced and

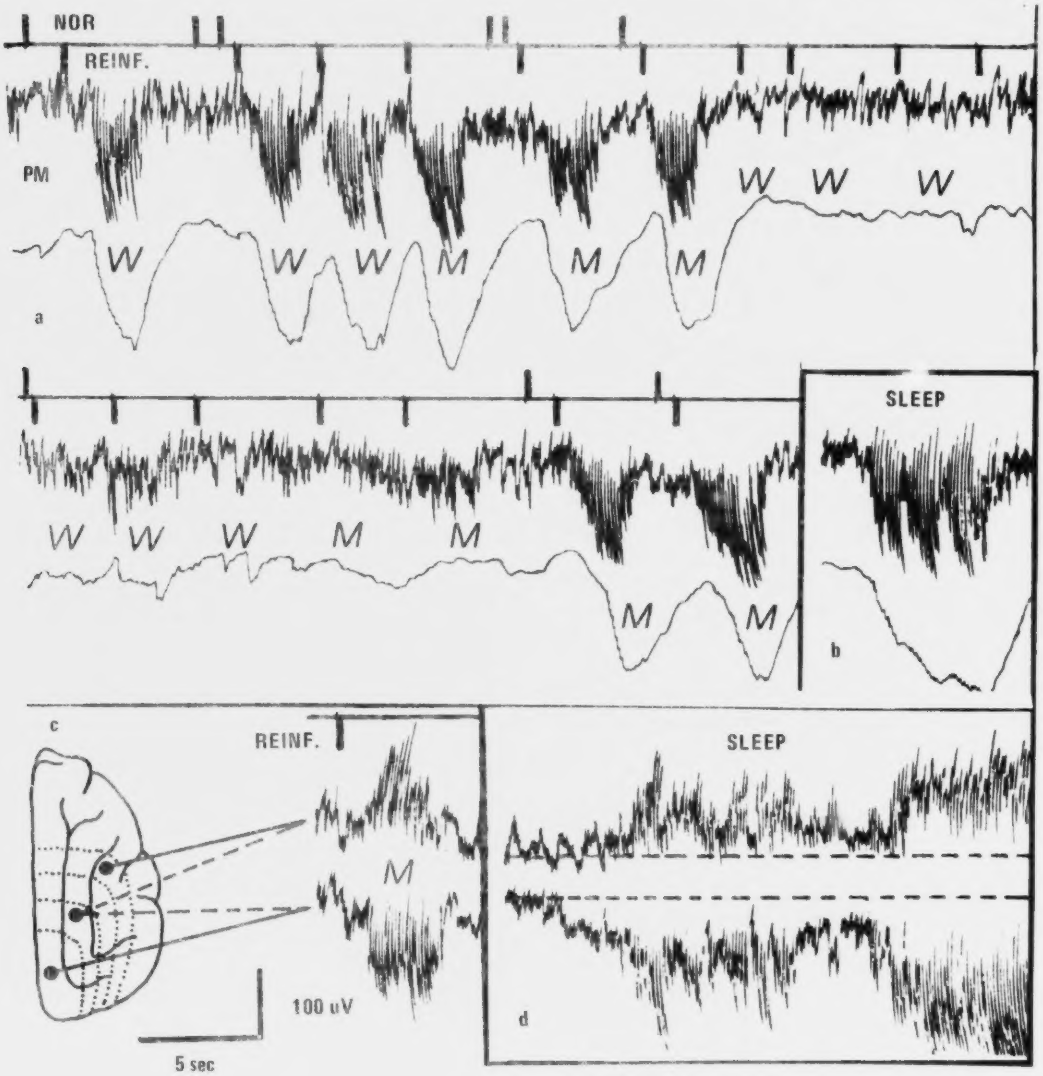

Fig. 3. Sensitivity of reward contingent positive variation (RCPV) in the cat to changes in the quality of anticipated reward. a. On a variable interval schedule, 0.5 cc of water (W) or milk (M) was presented after a bar press. NOR, nonrewarded bar press; REINF, rewarded bar press. PM, recording over posterior marginal gyrus (striate cortex) referred to medial suprasylvian gyrus, as shown in c. Lower tracing in a and b filtered to half-amplitude response at 3 c/sec. c. Mirror reversal patterns of RCPV in bipolar recordings over PM and anterior ectosylvian gyrus with reference to medial suprasylvian gyrus, a phenomenon caused by a decreasing potential gradient of RCPV in the anterior lateral direction from the locus of maximum aplitude over PM. Note similarity of RCPV with sleep onset positive SP in b and d. (Marczynski et al. 1969.)

perfected. Moreover, it must be preserved by strong inhibitory influences from the limbic system *(matching)* impinging on the BSRF-*selector* and ARAS immediately after a correct response. Fig. 3. shows the sensitivity of limbic inhibitory influences to unexpected changes in the results of a particular behavior. After a bar press rewarded with 0.8 cc of milk, cats show bursts of waxing and waning EEG synchronization consisting of 7 to 9 c/sec waves over the parieto-occipital region (Clemente et al. 1964), a phenomenon associated with a large positive SP shift termed Reward Contingent Positive Variation (RCPV) whose patterns are virtually identical with those recorded during sleep onset (Marczynski et al. 1969, 1971a). A lesion in the basal forebrain region encompassing the limbic descending pathways blocks the occurrence of these EEG phenomena (Sterman and Wyrwicka 1967). Systematic studies of evoked potentials to auditory, somesthetic, and visual stimuli, showed that the processing of sensory input during reward-induced EEG phenomena is virtually identical with the processing of input during sleep onset (cf. Marczynski 1972). Electrical stimulation of basal forebrain areas along limbic descending pathways may produce a stimulus-bound sleep (cf. Sterman and Clemente 1962, Sterman and Wyrwicka 1967), and suppression of single unit activity in the ARAS (Lineberry and Siegel 1971).

In man during performance in a typical CNV paradigm, the CNV is often abruptly terminated by a long-duration positivity (e.g., Otto and Leifer 1973, Hablitz and Borda 1973, Loveless and Sanford 1973), which may reflect a transient but powerful inhibition of the BSRF-ARAS system. This interpretation is also plausible for the positivity that follows the CNV-like potential in paradigms that do not require motor response but only performance of a mental task (Donchin et al. 1973). The positivity observed after S1 in the CNV paradigm, including most P300 waves, may be triggered by a cognitive process based on matching sensory input with a "template" generated by the *indication of goal* and limbic system, a process resulting in transient but strong suppression of the ARAS. This interpretation is compatible with the suggestion made by Squires et al. (1973) and Sutton et al. (1973) that the P300, in most instances, results from "resolution of uncertainty".

Cooper et al. (this volume) described a large positive SP over the vertex and occipital cortex. This SP is associated with detection of an anticipated visual event, and it occurs prior to motor response. The duration of approximately 1 second indicates that this SP could not have resulted from a discharge of neurons and cortical "sink" for current flow. Instead, this SP probably resulted from hyperpolarization of a large population of neurons triggered by a transient suppression of the ARAS (see below). Convincing evidence for response-induced suppression of the ARAS and inhibitory nature of the surface positive SP of longer duration, comes from the study of Skilled Performance Positivity (SPP) of Papakostopoulos et al. (this volume). SPP is maximal over the vertex and encompasses the Rolandic area. It is preceded by an unusually large *Bereitschaftspotential* and is observed in healthy volunteers asked to perform a manipulative task demanding precision and gradual improvement of performance by providing real-time information about the outcome. It is apparent that this paradigm strongly engages the function of the *indication of goal* (frontal association cortex) and *matching system*. The most important aspect of SPP is the accompanying high-voltage, waxing and waning, 9- to 11-c/sec EEG oscillations over the same region. In view of what is known about the synchronization process (see below), such as alpha-like burst and slow potential could not emerge without transient but powerful suppression of the BSRF-ARAS system.

Hippocampal projections to the cortex

In order to generate specific spatiotemporal patterns of neuronal activity and retrieve learned behavioral modes or find solutions to pure mental tasks, the *matching* (i.e., categorizing) substrates must be promptly converted to a *retrieval* system under the influence of the *indication of goal.* During this process the limbic system may send commands simultaneously to the *BSFR-selector* and to wide areas of neocortex via pathways described by Lorente de No (cf. Smythies and Adey 1970) and marked as a bifurcating axon of the hippocampal pyramidal cell *(matching)* in Fig. 2. Following Kornhuber's view (1973), it must be emphasized that in man the limbic projections to neocortex that emerge from the classical Papez circuit (not shown), particularly those that relay in dorsomedial thalamus and frontal association cortex and then project to the ideational speech area of Wernicke, are essential in both the *matching* and *retrieval* processes. Hence, by projecting the relatively stable stream of "visceral" input to the cortex, the primordial categorizing and retrieval system sketched in Fig. 2, achieved an enormous level of sophistication. Correlational studies of EEG theta waves in the hippocampus and entorhinal cortex during learning in animals suggest strong limbic influences on cortical transactions, a process that is reversed after learning (Adey et al. 1961). These limbic - cortical transactions are modulated by nonspecific brainstem-thalamocortical projections (see below). Topographically restricted SPs monitored from the skull almost certainly result from these transactions.

ARAS control of thalamocortical synchronization and positive SPs

The function of recurrent inhibitory circuits present both in specific thalamic relay nuclei (cf. Andersen and Andersson 1968) and in cortex (cf. Steriade and Deschenes 1973) is inversely related to ARAS inhibitory modulation of inhibitory interneurons, as shown in Fig. 2. Although there is still no direct evidence regarding the nature of the inhibitory transmitter involved in ARAS suppression of inhibitory interneurons, there are some indications that these ARAS projections may be catecholaminergic (cf. Marczynski, this volume). On the other hand, it is almost certain that the transmitter released by inhibitory interneurons is gamma-aminobutyric acid (GABA) (cf. Krnjevic 1974).

Emergence of alpha-like oscillations in the EEG depends on two factors, reduced tonus of the suppressant action of the ARAS on R and inhibitory interneurons, and a sufficient barrage of sensory input to drive the recurrent inhibitory circuits (cf. Anderson and Andersson 1968). If the sensory barrage is insufficient, alpha activity can be restored in a stimulus-bound manner by electric stimulation of the lateral geniculate (Rick and Marczynski 1978). Corticofugal activity, e.g., activation of motor cortex, also may provide electromotive energy to initiate the function of recurrent inhibitory circuits immediately after an abrupt withdrawal of ARAS influences. It appears that tonic facilitory influences of the cholinergic ARAS on sensory transmission in thalamic relay nuclei are necessary for alpha emergence over wide cortical association regions, since antimuscarinic drugs, such as atropine or scopolamine, are known to block these EEG patterns. After smaller doses of these drugs, the bursts of alpha become "choppy" and are intermingled with irregular delta waves that most likely result from irregular "idling" of recurrent inhibitory circuits (cf. Marczynski and Burns 1976), a state which can be overcome by electric stimulation of the lateral geniculate (Marczynski, unpublished).

An important aspect of the thalamocortical phasing of neuronal activity is that only about one-third of the neurons actively participate in the recruitment of inhibitory circuits, as evidenced by rhythmic sequences of IPSPs and post-inhibitory discharges. The rest of the neuronal population remains hyperpolarized and silent (cf. Watanabe et al. 1966, Andersen and Andersson 1968, Marczynski and Karmos, this volume). At the cortical level, hyperpolarization of larger pyramidal cells results in a positive wave (Watanabe et al. 1966). Similarly, hyperpolarization of neurons in subcortical structures is also reflected as a local positive SP (cf. Skinner, this section; Marczynski, this volume).

A relatively small change in rhythm of sequential IPSPs affects the inhibitory process. A study of the recovery cycle of two sequential IPSPs triggered in feline visual cortex by stimulation of afferent pathways (Watanabe et al. 1966) showed that a time interval of 130 msec between the onset of two IPSPs is optimal to obtain partial summation and maximum hyperpolarization. This interval corresponds to a 7.7-c/sec high-voltage EEG pattern normally observed in unrestrained cats during sleep onset or in a fully alert animal after a rewarded bar press during the emergence of RCPV (Marczynski et al. 1969, 1971a). Thus, it appears that the thalamocortical system is "using" the most effective rhythm to produce inhibition. Data of Watanabe et al. (1966) show that a 20-msec reduction or increase in the time interval between sequential IPSPs (corresponding to a 1.4-c/sec change from the 7.7-c/sec rhythm) would result in approximately 40% reduction in hyperpolarization. A similar conclusion can be drawn from a study of the RCPV and the topographically restricted sleep onset positive SP in the cat induced by flash stimuli at various frequencies (Marczynski et al. 1971a, Marczynski and Sherry 1972). There is no reason to believe that the basic neurophysiological characteristics of the feline thalamocortical system are different from those of man. Hence, the seemingly small shifts in the power spectra of alpha patterns and their "choppy" character in schizophrenic patients, coupled with suppression of slow-wave sleep delta patterns (cf. Itil et al. 1972), could reflect a substantial loss of the inhibitory capacity of the thalamocortical system.

Another interesting aspect of thalamic recurrent inhibitory circuits is that they are capable of converting a totally patternless (i.e., "noisy") sensory input, devoid of any conceivable informational properies, into an effective and most likely meaningful inhibitory process (Marczynski et al. 1971b; cf. Marczynski and Burns 1976; Marczynski and Karmos, this volume; Rick and Marczynski 1978). Discussion of this topic is, however, beyond the scope of this article.

Basic modes of operation of the thalamocortical system; diffuse vs. localized EEG and SP patterns

Despite the diffuse character of cholinergic and catecholaminergic projections from brainstem nuclei to the midbrain, forebrain, and neocortex (cf. Hockman and Bieger 1976), these ARAS components are essential in generating topographically restricted EEG patterns and SPs. Recent studies of the role of the *nucleus reticularis thalami* (R) (cf. Skinner, this section) have clarified the contradictions by showing that specific parts of R send inhibitory axons to particular regions of sensory thalamic nuclei, thus selectively gating sensory input of one or several modalities. Furthermore, the spatial and temporal patterns in activation of R neurons are determined by impulses coming from fronto-orbital cortex, which is one of the main modulators of *indication of goal.* (For simplicity, inhibitory influences of the caudate nucleus will not be discussed and are not shown in Fig. 2). The contrast enhancing inhibitory background for excitatory influences of frontal cortex on R that may result in selective attention is provided by tonic hyperpolarizing ARAS influences (via catecholaminergic projections?), impinging on R and other inhibitory interneurons located outside R and in neocortex (cf. Steriade and Deschenes 1972, Andersen and Andersson 1968). Furthermore, the cholinergic component of the ARAS facilitates transmission of sensory input at the thalamic and cortical level, and thus further sharpens the contrast among "selected" specific projections (cf. Marczynski, this volume). The interplay between these influences may result in several alternatives.

Strong activation of the cholinergic and catecholaminergic ARAS would result in hyperpolarizing blockade of R and inhibitory interneurons, and lead to inactivation of recurrent inhibitory circuits. A strong facilitation of sensory input in all modalities would be associated with desynchronized EEG patterns, strong arousal, and diffuse negative SPs over the cortex and in specific thalamic nuclei. On the other hand, a dc electrode in R would show a large positive SP (see Skinner, this section). In such a state, the modulation of R by excitatory barrage from fronto-orbital cortex *(indication of goal)* would not be effective since it could not override the ARAS-induced inhibition. Selective attention would be blocked, and abstract thinking markedly impaired. The release of acetylcholine from the cortex would be markedly increased, but the release of GABA would be totally blocked (cf. Marczynski, this volume).

Mild activation of the ARAS, with a slight predominance of the cholinergic component, would provide a background for most complex and selective transactions at all lavels. Mild suppression of R by the ARAS could easily be overriden by excitatory influences from the frontal association cortex, which could generate highly specific spatio-temporal excitations of modality-specific loci in R. The latter, in turn, would selectively modulate the function of thalamic relay nuclei. Only those thalamic nuclei or parts thereof that are not blocked by R would show increased neuronal activity and a negative SP. Corresponding cortical projections would also show negative and topographically restricted SPs associated with increased unit activity and desynchronized EEG patterns. The activation of cortical association projections would further determine SP topography. Recurrent inhibitory circuits in the cortex and thalamus could be readily activated or show only moderate involvement because of the suppression of inhibitory interneurons.

After successful performance of a motor or mental task, basal forebrain and limbic influences would suppress the ARAS. This suppression would lead to vigorous activation of recurrent inhibitory circuits, mainly or selectively in those thalamocortical projections exempt from R inhibition, because only in those regions would there be sufficient synaptic drive to activate recurrent inhibitory circuits. Hence, in most instances, substrates that, prior to the response or mental problem, showed a negative SP and desynchronized EEG patterns would dramatically shift toward EEG synchronization of the alpha type and a strong positive SP (e.g., Skilled Performance Positivity or RCPV in animals). In cortical areas which receive only weak sensory input, such as motor cortex, activation of pyramidal tract neurons during task performance could also be promptly converted, via axon collaterals, into vigorous activation of recurrent inhibitory circuits immediately upon task completion. This sequence of events and ARAS suppression would lead to the emergence of a strong positivity associated with EEG synchronization. The positivity observed after the CNV may belong to this category.

In this context, long-lasting positivity, maximal over the post-central region, observed during sustained motor response (Otto et al. 1974) is difficult to explain. If sustained contraction of the hand (most likely involving some muscles of the forearm and shoulder) is, however, associated with massive discharge of neurons located deep in the central sulcus, then the deep negativity caused by depolarization of neurons, apical dendrites, and glia cells would constitute a strong sink for current flow from surrounding areas that should be reflected as positivity at the vertex. Distribution of SPs in animals supports this interpretation (Marczynski et al. 1971a), since a strong positivity over the striate cortex ranging from 200 to 400 μV measured epidurally constitutes such a strong "source" for current flow that surrounding cortex, e.g., the ectosylvian or the anterior suprasylvian gyri, shows a smaller but consistent negative SP. The mechanism for such a reversal of SP has been discussed elsewhere (Marczynski et al. 1971a).

Selected aspects of ARAS influences on cortical function and evoked potentials: A new working hypothesis

The basic theory of evoked potentials (EPs) has been discussed before (Creutzfeldt et al. 1969; McSherry 1973; Marczynski, this volume). As shown in Fig. 2, the interplay between excitation and inhibition induced by cholinergic and catecholaminergic projections, respectively, is of primary importance. The depolarizing and profuse cholinergic terminals seem to be concentrated on cell bodies and, possibly, dendrites of large pyramidal cells of layers 4 and 5. These cells are endowed with "pure" muscarinic receptors (cf. Krnjevic 1974). The distribution of noradrenergic and catecholaminergic terminals is not yet defined, but it seems logical to assume that a catecholaminergic input is provided to gaba-ergic inhibitory interneurons. Indirect evidence for catecholaminergic modulation of the inhibitory neurons of R is reviewed elsewhere (Marczynski, this volume).

The presence of dopaminergic terminals in neocortex (Thierry et al. 1973) and the potential interaction of such terminals with cholinergic postsynaptic receptors of pyramidal cells and dendrites may be of primary significance in understanding pathognomonic aspects of EP changes observed in schizophrenics (cf. Shagass 1976). The role of the dopaminergic system in the etiopathogenesis of schizophrenia is well established (cf. Meltzer 1976). Studies of the interaction between dopaminergic and muscarinic cholinergic receptors in the autonomic ganglia (Libet, this volume) have shown that dopamine dramatically enhances and prolongs cholinergically mediated depolarization of the postsynaptic membrane.

Extrapolating to the cortex, one could predict that an increased tonus of the dopaminergic system would prolong and impair the recovery of the membrane potential of cholinoceptive pyramidal cells and dendrites which to a large extent determine EP patterns. This mechanism would account for several well-established observations in schizophrenic patients, such as reduced amplitude recovery of somesthetic, auditory, and visual EPs (Shagass 1976); lower CNV amplitude (Dongier 1973, McCallum and Abraham 1973) due to tonic depolarization of apical dendrites; and prolongation or even lack of recovery of the CNV and the post-imperative negative variation (PINV) (Timsit-Berthier 1973, Dongier et al. 1974).

The prolongation of the spiral aftereffect (Herrington and Claridge 1965) also belongs to the same category of phenomena. Callaway et al. (1965) found that greater variability in the waveform of EPs in schizophrenics correlated with degree of thought disorder, but not with other symptoms such as changes in affect or cooperativeness (Jones et al. 1966). This finding may also be explained by greater variability in the recovery of membrane potentials "sensitized" to acetylcholine by an excess of dopamine or by a genetically determined misplacement of dopaminergic terminals.

With the consolidation of the "dopamine theory of schizophrenia" (cf. Meltzer 1976), there is a tendency to believe that the dopaminergic projections to the limbic and mesolimbic structures (such as nuc. accumbens, amygdala, and hippocampus) are the main culprits. This view, disregarding the neocortical mechanisms, may be a greater oversimplification than that committed by this author in sketching a model of the mammalian brain.

Ed. Note: A further paper relevant to the subject of neurophysiological models by Dr. Benjamin Libet entitled "Slow Postsynaptic Responses of Sympathetic Ganglion Cells as Models for Slow Potential Changes in the Brain" appears earlier in this volume in the Electrogenesis Section.

INTEGRATIVE MODELS: MACROPOTENTIALS AS A SOURCE FOR BRAIN MODELS

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Brain macropotentials are products of at least three factors: the experimenter's interests, the subject's brain, and available technology. Because technology is a matter for straightforward description, we can, with some slight risk, omit it from discussion and concentrate upon the remaining two factors.

The impact of the experimenter's interests and the way in which he defines his variables have a more insidious impact upon what he records and how he interprets his results. As Donchin (1973) points out "...all too often the relationship between the author's conclusions and his data are tenuous, due to absence of critical control conditions or to ill-chosen critical parameters." Even earlier, Sutton (1969) presented a "partial list of psychological terms for which evoked potential correlates have been reported" and commented "It is difficult to believe that all these findings involve genuinely different potentials. The problem posed by a plethora of cross-cutting, poorly defined concepts is not a trivial one. First, they make claim to a level of generality from which one can only retreat. Second, they make a poor foundation for moving forward since progress will depend less on the broadness of the claims and more on the precise control and specification of experimental operations and on the precision of reasoning involved in attempts at construct validation."

If we are to improve upon this rather poor performance, we must first examine two important issues: (1) the characteristics of the electrophysiological events with which we work and (2) the levels of analysis we employ in our descriptions.

Macropotential Characteristics

We may be guilty, in the field of human macropotentials, of creating an elaborate language without adequately defining or understanding the basic elements of that language. This lack of definition of fundamental characteristics of macropotentials is perhaps the greatest single obstacle to the formulation of an effective theoretical model; however, the deficiency has not passed entirely unnoticed.

For example, one basic characteristic of macropotentials is taken to be their amplitude, yet Brazier (1964) demonstrated the ambiguity that may underly amplitude measurement in average evoked potentials. The cause may be either the time jitter, which occurs across individual trials, or the differential change in amplitude of particular components as the experiment proceeds. Papakostopoulos (1973) demonstrated this latter type of change in the first and second late negative components of the tactile EP using recording from prefrontal cortical areas. EP components have also been shown by Walter (1964) and Remond (1964) to vary according to ongoing, intrinsic brain activity at stimulus onset. Pfurtscheller and Cooper (1975) have shown that activities of cortical areas far apart as well as local intrinsic activity can influence the latency of individual evoked potentials recorded from a particular cortical area with resulting amplitude ambiguity. In spite of these considerations, no systematic attempt has been made to rationalize or define amplitude measurement.

This lack of precision in delineating basic characteristics of macropotentials is at the root of our failure to formulate satisfactory theories about the brain based upon macropotential data. The tendency has been to treat macropotentials as if they were there to solve problems of brain connectivity or to provide a respectable neurophysiological dressing for vague anthropomorphic constructs, or to justify generalizations of principle derived from artifically created particulars.

Some fundamental re-thinking would at this stage seem advisable. We may assume that macropotentials are a basic property of the brain, as are weight, myelo-, or cyto-architectonics. Evoked potentials can be further characterized in terms of rise time, amplitude, and phase or latency. We can, on the basis of these parameters, begin to provide a descriptive framework or model of the brain.

Models are used by different people for different purposes. A common use, cited by Lachman (1960), is "the reproduction of the theoretical prototype in terms of mental pictures or images." Others regard this type of model building as a weak and scarcely reputable exercise. Yet this is not the only function models can fulfill. They can be used as bases for inference and interpretation. The model of the servo-control of movement (Merton 1953) is such an example. The known neuroanatomical and neurophysiological data about the neuromuscular system were taken into account in this model of voluntary contraction. The proposed model suggested indirect initiation of contraction by activation of muscle spindles, which in turn activated the stretch reflex. However, more than a decade later, data were presented by Valbo (1971) which indicate direct activation of muscle fibers before any change in the rate of firing of spindles. The original model was modified accordingly, and a new servo-assistance hypothesis was proposed (Mathews 1972). The useful lifespan of the new model will depend upon the extent to which data from the experimental research it generates either support or refute it (Valbo 1971, Merton 1974).

This particular model was chosen as an example because it has been used successfully in stimulating and guiding research. It has led to new discoveries both in animals and man over a long period of time and has been applied at both the micro- and macro-levels of the neurosciences. Another reason for the choice is the relatively limited experimental area from which the basic facts were derived. The model did not encompass either controversial questions about the significance of sensory input for movement initiation or the complex spatiotemporal patterns of brain-body organization, each of which is a prerequisite of adaptive goal-directed motor activity. The model was successful because it was well defined and thus amenable to experimental verification or refutation, not because it was complete or because it proved correct.

The lesson to be drawn is that any model of the brain, in health or disease, that is to be based upon macropotentials has to be preceded by a clear definition of the characteristics of those macropotentials. That is to say, we must first clearly specify the basic elements of our language.

The search for an adequate language of the brain having its basis in macropotentials and their characteristics can perhaps be discerned in the use by Walter (1964) of such terms as "modality signature" and "dispersive convergence." More recent emphasis on waveform and distribution to interpret the functional significance of evoked and slow potentials could be interpreted as a step in the same direction.

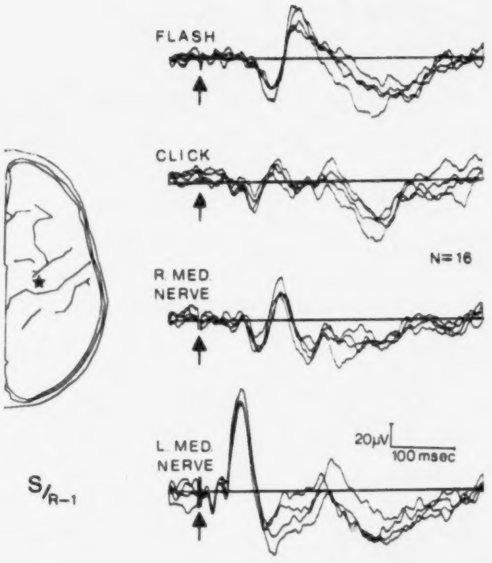

Fig. 1. Superimposed average evoked potentials corticographically recorded in man from an electrode precentrally located on the right hemisphere (star) and referred to a common average reference electrode. Time of stimulus presentation indicated by arrow. Potentials shown following visual (FLASH), auditory (CLICK), ipsilateral (R. MED. NERVE), and contralateral (L. MED. NERVE) median nerve electrical stimulation.

Levels of Analysis

The waveform recorded with a macroelectrode is multidimensional in terms of both its origin and its description—in terms of origin because thousands of neuronal elements contribute to its generation and in terms of description because the macropotential can be approached from different levels of analysis. These analysis levels can, for convenience, be subdivided into local, time, and spatial.

Local Level

Subdural macroelectrodes chronically implanted in man have revealed four specific characteristics of brain electrical activity:

1. *Local polymorphism:* From a particular cortical electrode, many or all the main types of macropotential can be recorded. For example, from one precentral electrode intrinsic activity, sustained, and evoked potentials to stimuli in various sensory modalities can be recorded. The latency and waveform of the latter vary according to modality (Fig. 1).
2. *Regional reactivity:* Under certain conditions the potentials of certain areas diminish to a point

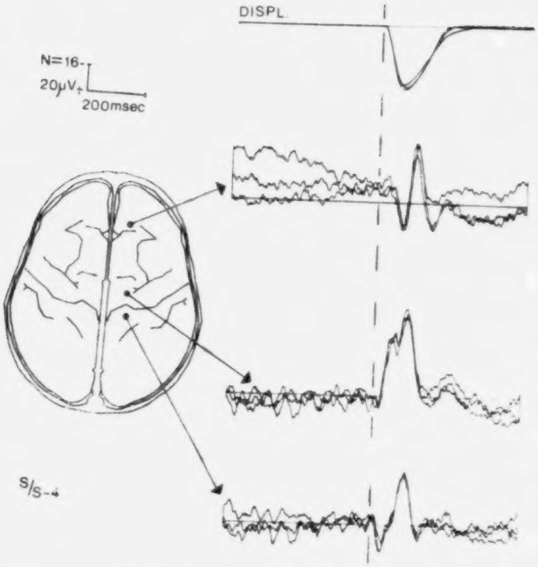

Fig. 2. Superimposed averaged evoked potentials corticographically recorded in man and following left index finger externally paced displacement (DISPL.). Electrodes located in prefrontal (upper traces), precentral (middle traces), and postcentral (lower traces) cortex.

at which they cannot be differentiated from noise, although the potentials of adjacent areas are still recordable (Papakostopoulos et al. 1975).

3. *Component independence:* Certain components of an EP waveform can be localized or generalized according to behavioral conditions. A typical example of this principle has been demonstrated with the behavior of the P300 component under go and no-go circumstances (Papakostopoulos and Crow 1976).

4. *Spatial specificity:* Intrinsic activity and EPs from brain locations a few millimeters apart can be different in frequency and waveform (cf. Freeman and Gerbrandt, this volume). EPs following finger displacement and intrinsic activities are shown in Fig. 2 and 3, respectively. On both occasions each area has its own characteristic activities. Yet these activities vary in different areas simultaneously registered.

Time Level

No EP occurs in isolation. At the instant an EP is recorded, other things are happening in the brain, a fact which, as Sutton (1968) pointed out, is often ignored by experimenters. Intrinsic rhythms, for example, go on continuously, as does modulation of membrane potentials. Even the pattern of neuronal connections has been demonstrated to be subject to continuous functional modulation (Purpura 1970, Scheibel and Scheibel 1970, Skinner, in press, Yingling and Skinner 1975). The brain is certainly no *tabula rasa* at the time of stimulus input. It has evolved to its present state as the result of species-specific and individual-specific interaction with the environment. Fig. 4 indicates schematically the influence of factors having their origins in both nature and nurture and of processes both overt and covert. All these influences are present in the processing of each stimulus, and their interaction and integration determine the outcome in response terms. Data are now available (John et al. 1973) that the waveforms of macropotentials reflect both the intrinsic significance of the present stimulus and the influence of previous stimulus configurations which were similar, but not necessarily identical.

Spatial Level

Discussion has centered around an electrode recording from a particular cortical location. The practice of considering activity at one location as if it existed in isolation can result in a form of intellectual blindness to the overall pattern of events. Several studies published recently deal specifically with the scalp distribution of EPs in most sensory modalities (cf. the scalp distribution section in this volume). Others have dealt with cortico-cortical relationships (Papakostopoulos and Crow 1976) and cortico-subcortical relationships (McCallum et al. 1973, 1976). Other evidence indicates that during each particular behavioral sequence both central structures and peripheral systems present consistent patterns of change. For example, heart rate decreases during the foreperiod of a simple reaction time experiment, i.e., during the period in which the CNV develops (Lacey and Lacey 1970, Papakostopoulos 1973). The excitability of the spinal monosynaptic reflex also changes during the same period (Papakostopoulos and Cooper 1973, 1976, and this volume). The total pattern of change in cortical, subcortical, spinal, and peripheral systems appears to be constant for any particular stage of the preparatory process, but it changes as the process moves towards its goal. The spatio-temporal description of performance can reasonably be considered the objective index of animal and human integrated interactions with the environment, and yet the dynamics of spatiotemporal processes that we are in a unique position to investigate have not so far been studied in depth.

Creation of a Model

What kind of brain models are indicated by the various factors discussed? What sort of experiments should we envisage? To which other disciplines and in what way should we look for relevant answers?

A brain model created from macropotential principles should take into account (1) the areal specificity,

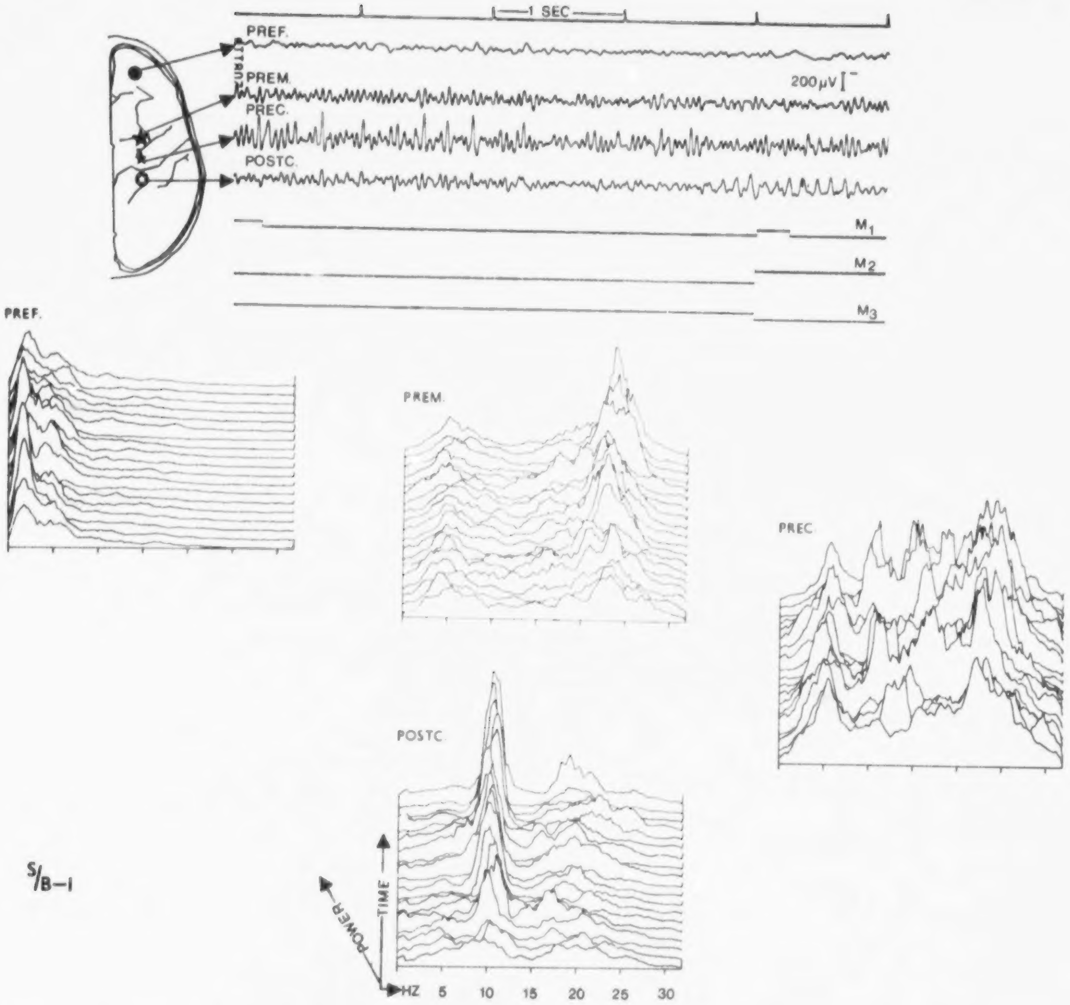

Fig. 3. Sample electrocorticogram (right hemisphere) and corresponding power spectra from prefrontal (PREF), premotor (PREM), precentral (PREC), and postcentral (POSTC) cortical areas in man. Each spectrum derived from 16 sec of ECoG activity; 19 spectra shown for each area.

(2) the areal plasticity, (3) the different spatial representations of each event, and (4) the different organization of the local and spatial relationships at every point in time. How, if at all, a sensorimotor event is going to be represented in the various local brain domains depends on the relative weighting of the numerous factors operating in the system at the time. Which factors shape the function of a domain, and what their value is set to at a given point in time will depend on past, present, or anticipated future input-output of the domain. Particular domains may have many, few, or no factors in common with other domains. If there are common factors, they may vary in unison or with varying degrees of independence in the different domains. The two modes of nervous function described in the model proposed by Cooper, McCallum, and Papakostopoulos (this section) presumably influence the setting of these factors.

E. Roy John's "neurometric space" (John et al., this volume) is a pioneering attempt to quantify the multifactorial reality of brain macropotentials. This approach adheres "to the fact that sensory, perceptual and cognitive processes, as well as the anatomical and functional integrity of the nervous system, are reflected in the electrical activity of the human brain as recorded with scalp electrodes." One can envisage that psychiatric or neurological diseases will be described in the future by their coordinates in such a neurometric space.

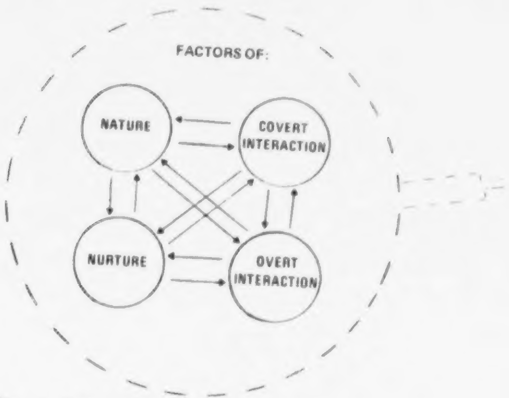

Fig. 4. Schematic of probable factors and their interactions with processes represented in the electrical activities recorded from a macroelectrode.

One can conceive of experiments addressed to fundamental questions about the quantification of each factor in particular, about the values of many factors in the spatial dimension of the organism, or about the principles of factor setting in time in one location or throughout the whole organismic space. In the first instance, diversity in experimental paradigms is desirable. The case of CNV amplitude at the vertex could be an example. What, for example, is the maximum value that the CNV can reach at the vertex and under what circumstances? We know that the amplitude can be substantially increased by interposing a signal between S1 and S2 in such a way that its location in time and its duration cause the subject continuously to revise the nature of his ultimate response to S2 (Fig. 5), but is this the optimum method for enhancing its value?

When studying such factors and their relationships in organismic space, rigidity of experimental paradigms is necessary. Small changes in experimental procedure can change the state of both brain and bodily systems (Papakostopoulos and Cooper 1973, 1976, and this volume).

The question of relationships with other disciplines has practical and theoretical implications. Practically, we must know something of the electrocardiogram or plethysmogram or myogram in order to set the characteristics of our amplifiers, or the sampling rate of our computer, when recording brain macropotentials. We should continue to bear in mind that the activities of neurotransmitters and neuronal loops lie beneath our macropotential configuration, but we should not be restricted to verifying hypotheses of brain function derived from such studies. There is no good reason to assume that a hypothesis derived from one restricted level of analysis can be applied to another, particularly when the latter reflects the total interaction between organism and environment. Harmon (1972) makes the point that "...in neurophysiology it seems hopeless to accept the standard argument that one must start at the lowest levels. ...Extrapolation in the other direction may, however, be somewhat easier. Knowledge at a higher level may help one develop strategy for investigation at a lower level." In other words, in our model-building we should work outward from our own phenomena. The function of macropotential research should be the creation of questions and hypotheses that can be tested at the unit, neurochemical, or psychological level of analysis.

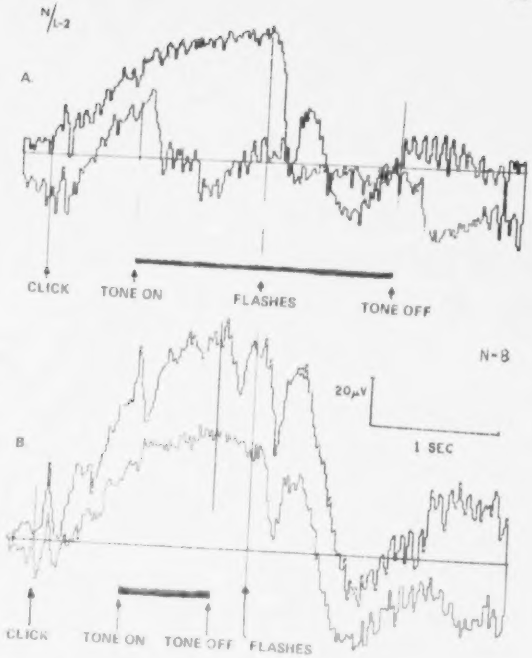

Fig. 5. Average vertex CNV from one subject in two different situations. A: Sit. 1 with CLICK as warning and FLASHES as imperative signal. In half of the trials a tone was interposed (black bar) and the subject had to withhold the response to FLASHES at the onset of the tone. Note the CNV termination either with the tone onset (TONE ON) or the motor responses to the flashes (upper trace).
B: Sit. 2 was as in sit. 1 except that the subject was told that if the tone terminated (TONE OFF) before the flashes, then he should not keep on withholding the response, but should press to the flashes. In spite of the complexity of the last situation, the obtained CNV (upper trace) was about twice the amplitude of CNV during the straightforward "press" trials (lower trace).

CHARACTERISTICS OF EVENT RELATED MACROPOTENTIALS

THE ROLE OF THE BEREITSCHAFTSPOTENTIAL AND POTENTIALS ACCOMPANYING THE EXECUTION OF MOVEMENT

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My approach can hardly be called a model, but it may clarify motor elements of event-related macropotentials. Discussion will be confined to the Bereitschaftspotential (BP) and to motor aspects of the CNV, although I appreciate that the CNV may not be explainable exclusively in motor terms. To me the exhortation that we should now be looking beyond phenomenological levels of description means that some thought and speculation should be addressed to questions such as what is the biological meaning of these slow potentials? What are the underlying mechanisms and what is their functional significance?

Kornhuber (1974) integrated slow potential changes into a model of motor function. I do not wish to repeat this theory in detail as it is well known, but I do wish to put forward the view that one of the classical concepts of motor organization has to be corrected. Despite the importance of work by Penfield and his colleagues (e.g., Penfield and Rasmussen 1950), they over-estimated the role of the motor cortex. Penfield's claim that all motor acts originate in motor cortex is, in our opinion, not true; almost all cortical areas are capable of motor acts. Stimulation of the motor or somatosensory cortex yields movement, but one can elicit movements also from parietal areas, and eye movements from frontal areas with somewhat higher stimulus strength. The motor cortex is a highly specialized structure for movements that require complicated tactile analysis provided by sensorimotor cortex, such as finger, lip and tongue movements. These movements are represented primarily in the motor cortex, but others that function well without tactile analysis, e.g., eye movements, are not represented there.

Let us start with the electrogenesis of slow potentials, make the crucial assumption that CNV and Bereitschaftspotential are negative shifts of the cortical d-c potential, and then consider which general influences cause shifts of the cortical d-c potential. There are many such influences, ranging from metabolic and physiological to psychological factors. Hyperoxia produces a negative shift; hypercapnia, a positive shift (Caspers and Speckmann 1972). Increasing wakefulness leads to a negative shift; falling asleep is accompanied by a positive shift; and arousal reaction in the EEG is associated with a marked negative cortical d-c shift (Caspers 1963, 1965). In freely moving animals, negative shifts occur during orienting responses to certain stimuli (Arduini 1957). Pharmacological studies show that narcotics, sedatives, and GABA cause a positive shift, while amphetamines cause a negative shift (O'Leary and Goldring 1964). On the basis of these observations, we may conclude that negative d-c shifts are usually associated with activation and positive shifts are usually associated with inactivation or inhibition. This view is further supported by intracellular data from Caspers and Speckmann (1972) who found that negative shifts of steady potentials are associated with increased EPSP rates of cortical neurons and that positive shifts are accompanied by decreased EPSP rates.

This evidence suggests that cortical d-c potential shifts provide a fairly reliable indicator of cortical state. Both CNV and Bereitschaftspotential represent shifts of the cortical steady potential. If we use them as indicators in the above sense, we can infer which cortical areas are active in relation to a particular goal. I regard both Bereitschaftspotential and CNV as *early preparatory processes*, and I infer that they represent a facilitatory cortical process taking place in the dense dendritic network of upper cortical layers. I also believe that this facilitatory process is specific and highly selective to the extent that one can tell from the topography of these potentials where the action is or where it will be in the intended task.

Recent experimental evidence from the Bristol group (McCallum et al. 1976), from Rebert (1972), and from Skinner and Lindsley (1973) suggests that the early preparatory process of CNV and BP is not exclusively a cortical phenomenon, but a thalamocortical phenomenon. It becomes possible to envisage a thalamocortical focus of activity that shifts over the cortex depending upon the site of action. This thalamocortical focus of activity is constantly changing–i.e., it projects to speech centers during speaking, to the right parietal region with constructive or spatial tasks, to the visual area during attentive visual perception, and to the frontal areas with decision. In order to record this focus of activity with present methods, we tend to keep our experiments as constant and stereotyped as possible with the result that this focus is frozen in one position. I think we can assume that this early preparatory process also occurs preceding thoughts, intentions, ideas, and other cognitive or volitional acts, which unfortunately as yet cannot be transformed to a trigger pulse. I was speaking of the early preparatory process of the CNV and the readiness potential in the same sense and indeed it is my opinion that they represent the same underlying mechanism. The CNV differs from the BP in (1) the experimental situation producing it, (2) waveform, (3) topography, (4) relative bilateral symmetry, and (5) possible independence from motor acts (cf. Deecke et al. 1976, p111f.). These differences are of a merely operational nature and represent modifications of the same underlying early preparatory process.

The constantly changing thalamocortical focus of activity associated with these early preparatory processes may be called a type of arousal, alertness, or attention, but the term should not be taken to imply that such processes are nonspecific; on the contrary, they are highly selective. Even such basic processes as regional cerebral blood flow are highly selective (Risberg et al. 1975). When the subject performed a verbal test, regional blood flow was increased in the left hemisphere; when he performed a spatial test, it was increased in the right hemisphere. Thus, even basic vascular and nutritional processes are to some extent selective and many kinds of dynamic changes going on in the living brain are more specific than we think. Experiments with the emphasis on topographical evaluation of slow potentials are needed because slow potentials reveal, more effectively than faster potentials, which brain regions are active in a given experimental situation.

In conclusion, the potentials preceding a voluntary act, such as a finger movement, that must be taken account of by any theoretical model are essentially of three kinds: (1) an early preparatory process - the Bereitschaftspotential – recordable as a slow negative shift of the d-c potential, (2) a faster potential – premotion positivity (PMP) described by Deecke et al. (1969), and (3) the motor potential (MP) proper. The latter potential is a unilateral potential that precedes unilateral finger movement (but not eye movement) with a mean onset time of 60-50 msec prior to the first EMG activity. It should, however, be noted that other workers, notably Vaughan et al. (1968), have used the term "motor potential" to refer to the whole complex of BP, PMP, and MP. The MP, as we define it, is a negative-going potential recorded over the motor cortex contralateral to movement and most probably reflects cortical activity associated with the ongoing pyramidal tract volley (cf. Evarts 1966). The temporal relationship of the MP and movement led us to postulate a cortico-cerebello-cortical loop preceding voluntary movement (Deecke et al. 1973, 1976), a feature confirmed in monkey experiments by Thach (1975).

THE PLACE OF CONSCIOUSNESS IN BRAIN RESEARCH[1]

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The question as to the kind of model or models we should use brings to my mind the broader question of how the purpose of brain research is best defined. Indeed, the adequacy of models is ultimately judged with respect to how well they aid in achieving specified goals. In this sense, there is not just one kind of model. The models (this section) of Deecke, Skinner, and the Bristol group, for example, may each be appropriate to the questions asked by the respective authors.

Research is commonly classified into categories of practical or clinical utility, on one hand, and intellectual understanding, on the other. Models discussed in this paper are of the latter kind. In broad terms, the central theoretical question of brain research is to understand how the brain does what it does. This includes many things, such as regulation of the endocrine system, water balance, body temperature, and breathing. The focus of this conference, however, is on psychological processes of the brain. I wish to propose that intellectual understanding of the psychological processes of the brain is of two kinds.

First, how does the brain produce and regulate psychological processes that occur outside of awareness? We are not conscious, for example, of how memory works. We have no subjective experience of the manner in which memories are constructed, stored, organized, and retrieved. Tricks can be learned to insure that certain material is adequately memorized (e.g., by rehearsal) and to retrieve certain items (e.g., remembering a person's name by thinking about places and events associated with that person). In this way, crude notions can be developed as to how memory is established and organized, but these notions are inferences and not direct experiences of memory processes. We also have no awareness of the mechanisms of perception, coherent thought, emotions or even the simplest voluntary motor acts. Although we have a profound ignorance of most of the psychological processes that underlie the mind, we nevertheless can use these nonconscious processes, and usually in effortless ways. We can make memory yield relevant portions of its contents, direct our thoughts to particular topics, or walk into the kitchen to make a cup of coffee. The system is somewhat analogous to a person who can drive a car and yet grasp virtually nothing of the means by which automobiles work. The theoretical significance of understanding the nonconscious psychological processes lies in comprehending the role they play in forming the contents of consciousness.

The second kind of understanding of psychological brain processes concerns those events of which we are conscious. The initial question here is how the brain produces consciousness, i.e., how biophysical events are transformed into personal experience. It was, I think, the sense that discovery of the significance of the mesencephalic reticular formation opened the door to understanding how the brain produced consciousness that gave the conference on *Brain Mechanisms and Consciousness* (Adrian et al. 1954) a special ambiance of excitement and achievement. Most brain scientists, however, limit their thinking to how the brain produces piecemeal, static contents of consciousness–i.e., how we see lines, geometric shapes, or colors; hear individual sounds; or have complicated percepts, such as a person's face. But the phenomena of consciousness go considerably beyond that. There is a flow and continuity of the contents of consciousness, so admirably described by William James (1890). When we are with a friend, it is not just a conglomeration of sensations or percepts that occurs: what we experience is that person. Taken in its broadest scope, the contents of consciousness constitute, for each of us, reality as we know it. Through a complex sequence of transformations and constructions (Neisser 1967), the brain produces the world we (consciously) live in, our personal identities, and the very

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[1] This work was supported by USPHS Grant HD 10804 to the author.

goals of comprehending how the brain does these things.

Some readers may wonder why two kinds of understanding have been proposed, since understanding nonconscious processes which provide the contents of consciousness might provide all the information needed. There are two reasons. (1) It may be assumed that nonconscious processes do not have conscious properties. (This is in contrast to Freud's view that the "unconscious" has conscious properties, such as wishes, aims, the ability to make judgments as to what should and should not enter consciousness, and the construction of strategies). (2) Conscious events have causal efficacy in brain activity of a different kind than nonconscious processes, because of their different properties (cf. Sperry 1969, 1970). Whatever the processes are that produce the experience of anger, for example, subsequent psychological events (both conscious and nonconscious) are activated and shaped by conscious properties of that anger. In other words, the flow of consciousness constitutes the reality in terms of which we think, feel and behave. Accordingly, the reality we experience affects the brain activities related to thinking, feeling, and behavior.

How should relevant models be evaluated?

Models should not be judged by the volume of research they stimulate. The models of Titchener and Hull, for example, produced vast quantities of data, most of which currently reside on dusty shelves. In recent years there has been a major shift in experimental psychology to information processing models of cognitive psychology. Since these models play a significant role in the search for event-related-potential concomitants of psychological processes, it is important to judge whether these models, and the research they prompt, will also one day find their way to dusty shelves. It is, of course, difficult to estimate the stability of particular models because of the current relative lack of knowledge concerning psychological processes and related brain events.

Since the position taken in this paper is that the ultimate goals of brain research concerned with psychological processes pertain to understanding the physiological mechanisms associated with conscious experience (cf. John and Schwartz, 1978), I propose that one essential way to evaluate relevant models is the degree to which they relate, at one point or another, to our own personal experience. This means that introspection must play an important role in providing basic notions of what it is we are attempting to explain, as I know of no other way in which it is possible to know what consciousness is or whether given lines of research are in any way related to conscious experience. The failure of Titchener's efforts was not that he used introspection, but that the kinds of specialized introspections his subjects were trained to perform were not related in any meaningful way to everyday conscious experience or to what consciousness is about: the construction of personal reality. As William James (1890) put it, "Introspective observation is what we have to rely on first and foremost and always." For a more recent, incisive statement of a similar position, see Bertrand Russell (1948, pp43-53). Using personal experience as a frame of reference, then, some comments will first be made on information processing models and then on event-related potentials.

Information processing models

The revival of interest in selective attention in the early models of Broadbent (1958) and other investigators brought to experimental psychology theoretical considerations that could readily be interpreted in terms of and related to experience. That we generally are conscious of only a limited portion of the environment, and usually some coherent portion, squares well with introspection. Investigations of the processes underlying selective attention, therefore, are immediately relevant to consciousness because such processes play an important role in forming the contents of consciousness. The work of Moray (1970), which showed that unattended material was not likely to enter long-term memory, whereas certain unattended words (such as the subject's name) could capture attention, was significant in that it spoke to the relevance of consciousness to memory and to the fact that unattended stimuli are processed to a considerable extent even though they may never enter consciousness. The key, as Sperling's (1960) work suggested, is that if attention is focused on a given subset of sensory input in such a way that it becomes conscious, then that input can influence other psychological processes, such as thinking, feeling, memory and behavior, whereas sensory input which is not attended lasts a few seconds at most and has no further influence.

The models and experiments that grew out of the information processing approach were a breath of fresh air after the dreary days of Behaviorism, where conscious experience was excluded as a relevant concern. Thus, where the purpose is to unravel the manner in which consciousness is produced, the early work of Broadbent and others provides relevant models.

A more recent model of information processing views attention as a capacity that can be "allocated" among various psychological processes (e.g., Kahneman 1973). Broadbent conceived of the mechanism of selective attention as a filter which, by admitting certain sensory inputs for further processing and excluding others, prevented overload of the system. While both models share the assumption of limited capacity, the allocation model views attention as a flexible process that operates at various states of information processing. Thus, attention can be directed to perception, storage in or retrieval from memory, imagination, or motor activities; and, attention can be allocated to more than one psychological process at the same time (up to some limit of capacity), depending on the amount of attention required for each operation. It is certainly possible to read a book and monitor crying from an infant in a nearby bedroom, but it is not likely that a book could be read while performing a vigilance task that required detection of minute changes in ongoing stimuli. Furthermore, in circumstances where complex activities are overlearned, such as walking or driving a car, it is possible to simultaneously engage in another complex process, such as conversation. These modifications in the concepts of attention also fit with introspection. Notice, however, an important change with respect to the fate of stimuli that do not reach awareness. In the earlier model, stimuli that do not reach consciousness decay in a brief period of time and have no further influence on other psychological processes. In the allocation model, stimuli that do not reach consciousness can influence behavior, in certain circumstances, as in driving a car; however, both models can include the idea that stimuli that do not reach awareness do not enter memory. Surely each of us has had the experience of doing something, such as driving a car or crossing a series of heavily trafficked streets, without paying (conscious) attention, and then suddenly become aware that for some time we had not been paying attention. In these circumstances, we usually do not have any recollection of the streets crossed or the road traveled. Thus, current experiments examining the manner and degree in which attention can be allocated among various psychological processes commend themselves for our purposes because they are related to conscious experience.

Event-Related Potentials (ERPs)

With the information models just described, in combination with personal experience, certain tentative conclusions can be drawn about the relationship between ERPs and consciousness. First, some ERP components can be related to conscious processes, whereas others can not. In auditory ERPs, for example, all components from brainstem potentials to N100 and P200 may be necessary for conscious perception of an auditory stimulus, but none is sufficient for conscious perception to occur. That is, a subject engrossed in reading or asleep, may be unaware of tones or clicks which nevertheless elicit these components. On the other hand, P300 seems to occur only when a subject is aware of the eliciting stimulus.

The work of Hillyard and Picton (in press) is pertinent. The demonstration that N100 is larger to stimuli in attended channels than in simultaneously presented unattended channels suggests two things. First, subjects seem to be able to consciously direct certain nonconscious psychological processes, reflected by the enhancement of N100, to select stimuli on the basis of simple physical characteristics. I say "direct" because it seems unlikely that N100 enhancement would occur unless a subject consciously intended to listen selectively to one channel over other channels and maintained that intention during stimulus presentation. If a subject's mind wandered, for example, and for a period of time he stopped selectively attending to the stimuli, N100 enhancement would probably disappear and N100 amplitude would be equal for stimuli of all channels. Second, a prediction can be made about the subject's attention on the basis of the relative amplitude of N100. Imagine telling a subject to count infrequent stimulus changes in one of two channels, but not to reveal which channel he intended to monitor. The relative amplitude of N100 should permit the experimenter to infer which channel had been attended, and to test the inference by subsequent questioning of the subject.

In terms of the so-called "cocktail party phenomenon," N100 findings suggest that subjects clearly hear stimuli in an attended channel, while stimuli in an unattended channel are perceived as background noise, analogous to the background babble of voices we experience at cocktail parties. Unfortunately, subjective reports have not been obtained (or reported) in these experiments. I am in full agreement with Tecce's remarks (this section) about obtaining subjective reports in appropriate ERP experiments.

The circumstance that P300 is elicited by infrequent changes in an attended channel and not in an unattended channel, suggests that stimuli in the attended channel are heard clearly enough so that infrequent, small changes in the attended channel are consciously perceived, whereas changes in unattended channels are not. It is not plausible to argue that changes in both channels are equally well perceived or that changes in an attended channel elicited P300 because they are task-related (are being counted) whereas changes in other channels are not task-related. If only one channel of stimuli is presented and subjects are instructed to press a key whenever they detect an infrequent, small change in stimulation, changes that are not detected do not elicit P300 (Ritter and Vaughan 1969). Presumably subjects are not aware of undetected changes. Subjective reports are of no use in this situation, since subjects cannot be expected to report changes of which they are unaware. Furthermore, when one set of stimuli is delivered while subjects are engrossed in reading, P300 is not elicited by small, infrequent changes (Squires et al. 1975). While it seems probable that subjects were not conscious of the changes in this experiment, subjective reports were not obtained. Finally, if subjects are reading or otherwise ignoring stimuli, changes obtrusive enough to capture a subject's attention do elicit P300 (Ritter et al. 1968, Roth et al. 1976). In the Ritter et al. study, subjective reports confirmed this conclusion. Thus, the weight of evidence suggests that P300 occurs only when a subject is conscious of the eliciting stimulus (or, to be more precise, when a subject perceives that a change in stimulation has occurred). Similar considerations apply to the slow wave reported by Squires et al. (1975) and the frontal P300 associated with complex, novel stimuli (Courchesne et al. 1975).

The bimodal model of Cooper and associates in this section can readily be related to the allocation model of attention. Note that Cooper et al. in evaluating this model make joint reference to "the experimental evidence and everyday experience." It is difficult to think of the CNV occurring without the conscious participation of the subject. The suggestion that the CNV is no longer elicited in warned, simple RT tasks when the task is so overlearned that conscious participation is no longer required to perform the task, is an intriguing way of interpreting the data. It is not clear whether relevant subjective reports were obtained from the subjects. If not, it would be desirable to do so since, as mentioned before, we can know when we have not been paying attention to some routinized activity.

In terms of the allocation model, subjects should have spare capacity when CNVs cease occurring if the bimodal hypothesis is correct. This could be tested, for example, by giving subjects an appropriate concomitant task at various points during the RT experiment. The prediction is that performance on the second task will improve in conjunction with stabilized RT performance, which is associated with absence of the CNV.

Conclusions

Information processing models appear to be useful in ERP research because such models can be related to personal experience and certain ERP components can be associated with conscious events. There are several ways in which ERP components may be related to consciousness: they may be influenced by consciousness, have an influence on consciousness, reflect consciousness itself in some way, or represent some combination of these possibilities. N100 enhancement to stimuli in attended channels, for example, presumably occurs because of conscious intentions of the subject to attend to a given channel. In this case, N100 enhancement demonstrates an influence of conscious processes on an ERP component. On the other hand, N100 enhancement may influence consciousness by playing a role in bringing stimuli of the attended channel to the center of conscious awareness and thereby increasing their clarity.

In terms of the bimodal model, the CNV in the "scopeutic" mode, may be thought of as being influenced by consciousness or perhaps even being a concomitant of consciousness. That the CNV occurs first and then engages the subject "scopeutically" in the task does not seem reasonable. Perception of the warning stimulus is more likely to activate conscious processes which direct preparatory events, in which case the CNV could be related to the conscious processes or to the mechanisms that underlie preparation. In the "categoric" mode, the warning stimulus presumably triggers the appropriate preparatory processes directly, without the intervention of conscious processes. Thus, no CNV is elicited.

The P300 is more ambiguous than N100 or the CNV in that all of the possibilities mentioned above could apply. P300 could affect the contents or quality of consciousness if it is assumed that P300 occurs prior to awareness of the eliciting stimulus. P300 may also be a correlate of conscious awareness (Posner 1975, Simson et al. 1976). Finally, P300 could reflect the effect of conscious awareness on nonconscious psychological processes pertaining to preparation for or strategies related to future events (Donchin et al. 1973, Picton and Hillyard 1974). Selection between the various possibilities (or some combination of them) awaits clarification of the functional significance of P300.

In summary, it seems fair to conclude that ERP research will contribute meaningfully to our understanding of conscious and nonconscious psychological processes of the mind.

SIGNIFICANCE OF SLOW POTENTIAL SHIFTS IN ANTICIPATION OF AND DURING TASK PERFORMANCE[1, 2]

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In discussions on the functional significance of slow negative shifts such as the CNV, one crucial aspect has received little comment–namely, that on many individual trials even with high-level task performance, no definite CNV can be observed in scalp recordings. Some relevant data from a study by Gaillard and Näätänen (1973) are shown in Fig. 1. Although the amplitudes of averaged CNVs were relatively large, many single trials, even with fast RTs, in a visual two-choice RT task were associated with no negative SP during the S1-S2 interval in the EEG record. Although people in the field may be aware of such data, the implications for the functional role of these negative task-related shifts in the behaving organism have largely been ignored. It is of crucial importance to our theorizing on the nature and role of SP shifts such as the CNV always to keep in mind that their existence – inferred from scalp recordings – does not appear to be a necessary concomitant of preparation or performance, even under conditions associated with well-developed averaged CNVs.

First let us consider the basic assertion that there really are trials with high level performance and no CNV. It could be argued that the CNV is not always observable on single trials for the same reason as for evoked potentials (EPs), namely that they are obscured by ongoing EEG activity. This argument is valid for EPs, but does not apply to slow potentials of average amplitude because the dominant EEG frequencies are of a similar order of magnitude as those of most EP components, but not of SPs[3]. The occurrence of spontaneous SPs, with a duration of one second or more, should be clearly observable at the scalp if present on any given individual trial. The only reason for a prominent slow negative potential to remain undetected in scalp recordings would be its temporal coincidence with a spontaneous positive SP of similar size, duration and distribution, such that the two events cancel each other. However, we find far too few examples of such positive SPs in our primary records to account for the lack of a negative shift in the EEG record on so many response trials. Hence we may conclude that CNV absence on individual trials is not merely the result of masking by other potentials. Trials really occur in which no CNV is generated in those same structures which, on the average, produce a well-developed CNV[4]. This inference cannot, of course, be made with regard to EPs.

What, then, are the implications if task-related SPs are not necessarily present during anticipation of, and preparation for, performance? This observation suggests that the processes giving rise to the generation

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[1] Supported by the Academy of Finland.

[2] The present discussion does not involve the slow negative frontal component (e.g., Weerts and Lang 1973, Loveless and Sanford 1974, and Gaillard 1976) and more specific processes such as Bereitschaftspotentials (cf. Deecke, this section) and those related to language production (e.g., Grözinger et al. 1976).

[3] The frequency of most spontaneous SP activity appears to be much slower (see Gaillard et al., in preparation) than that of task-related SPs recorded during inter-stimulus intervals or foreperiods of 1 second.

[4] If the "ceiling hypothesis" of CNV amplitude is valid, then some of the intra-trial variability of SP amplitude can, of course, be attributed to this factor. However, this hypothesis could by no means totally account for CNV absence on individual trials. For example, in trials 20 and 27 of Fig. 1, the baseline immediately after the foreperiod exceeds the CNV in negativity suggesting that a ceiling on negativity has not been in effect.

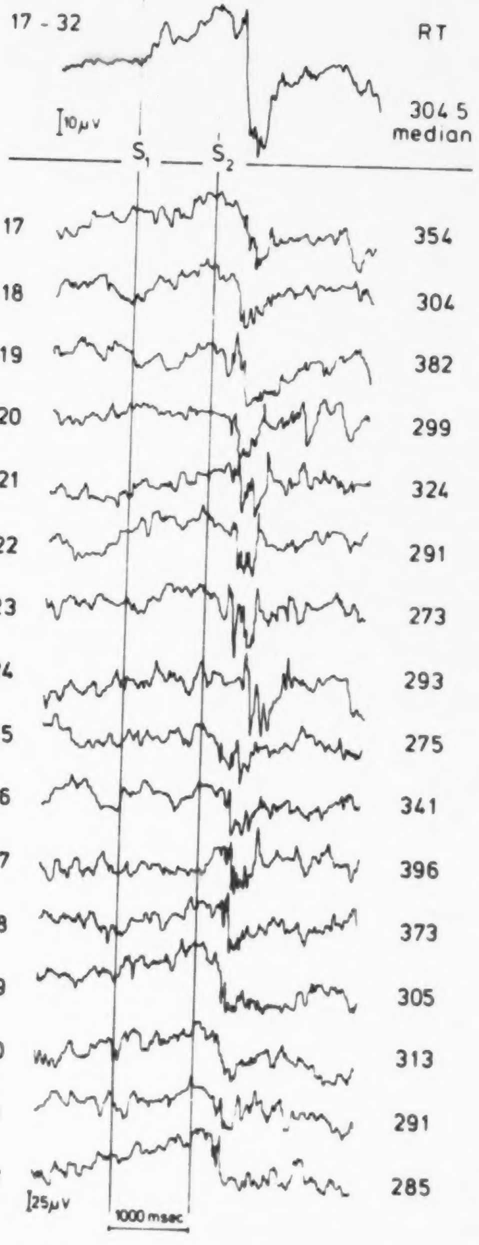

Fig. 1. Upper trace: Vertex CNV averaged over the 17th-32nd trial in a 2-choice RT task with an interstimulus interval of 1 sec. Data from the 2nd series of the 2nd session of one subject. Lower traces: Single vertex records of the upper trace (from Gaillard and Näätänen, 1973; reproduced with the kind permission of the North-Holland Publishing Company).

of negative shifts in the human brain are *temporarily coincident with, but not causally related to or contingent upon,* the physiological and psychophysiological processes necessary for a certain pattern of behavior. Hence SPs–at least as recorded from the scalp–would not be necessary to performance in the same compelling sense as, say, the activation of motoneurons is for movement. Many other CNS processes share the same property as suggested above for SPs. For example, EEG activation does not seem to be a necessary condition for good task performance (e.g., Dureman and Edström 1964). On the other hand, even a sleeping animal can have a highly activated cortex under certain drug conditions (Lacey 1967). In my evaluation of the inverted-U hypothesis of activation and performance (Näätänen 1973), I pointed out that the 'level of activation'–within certain wide limits–has not yet been shown to be an important determinant of performance. Lacey (1967) also cites numerous dissociations between behavioral and physiological events (e.g., Bradley 1958, Dureman and Edström 1964, Feldman and Waller 1962, Malmo 1966). These observations lead to the inevitable conclusion that much of present-day psychophysiological knowledge is at the level of temporal coincidences rather than causal relationships. Wikler (1952) observed similar dissociations between sleep states and EEG in atropinized cats. He concluded that "spontaneous electrical activity of the cerebral cortex reflects the activity of neuronal systems which, in part at least, are independent of those neuronal systems that subserve behavior in general" (p.265).

Feldman and Waller (1962) provide additional important evidence. Cats with nearly complete bilateral lesions of the posterior hypothalamus were somnolent and unresponsive to sensory stimuli, required tube feeding, showed no spontaneous movements, and could not be behaviorally aroused. Cortical desychronization, however, was easily produced by peripheral sensory stimulation or by stimulation of the midbrain reticular formation, even in the complete absence of behavioral arousal. The converse dissociation–a behaviorally aroused cat with a "sleeping" cortex–was produced by bilateral lesions in the midbrain reticular formation.

What then is the functional significance of CNV-like SPs in relation to overt behavior? To take a specific example, Tecce (1972) demonstrated that CNV correlates with attention, but we must not be tempted to infer that the relationship is more than a correlative one. We have already seen that task performance–which is frequently used as an index of attention–can occur in the absence of a negative SP. Present evidence does not permit an unequivocal determination of the psychological or behavioral dimension of performance which is reflected in scalp negativity. There is, however, some reason to think that conscious effort (as exemplified in situations of stress or "trying harder") might be the key.

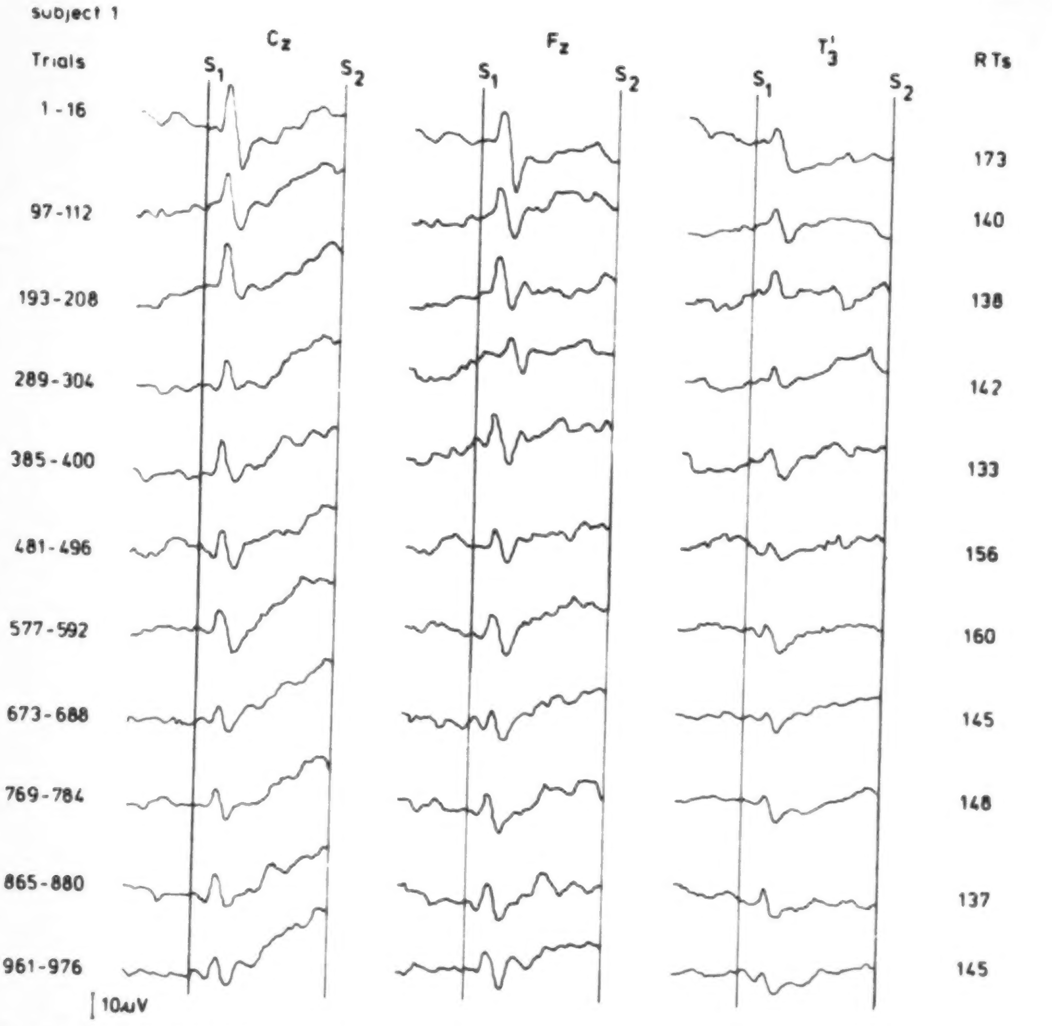

Fig. 2. The EP elicited by S1, the CNV and the median RT as a function of time for one subject in a simple RT task with an inter-stimulus interval of 1 sec and inter-trial interval of 5 sec. Derivations from left to right: vertex (Cz), frontal (Fz), and temporal (T3); negativity upwards (from Näätänen and Gaillard, 1974; reproduced with the kind permission of the North-Holland Publishing Company).

This interpretation seems to be consistent with the division of performance into "scopeutic" and "categoric" modes as suggested by Cooper et al. (this section). The former implies conscious, nonreflexive performance, associated with large negative task-related SPs. The categoric mode pertains to more automatic, less conscious behavior. This change would take place during the course of learning and would be associated with gradually attenuating SPs[5]. Cooper et al. suggest that the execution of performance in such circumstances is transferred to separate, second-order, semiautomatic systems in the brain.

According to these authors, individual trials showing little or no negative SPs should exist during the later parts of extended experimental sessions involving simple repetitive tasks. The authors' data showing habituation of CNV during a prolonged simple-RT experiment (Cooper et al. 1976) suggest this to be the case. However, Näätänen and Gaillard (1974) failed to observe any progressive CNV habituation in a simple-RT experiment with one-thousand trials (Fig. 2). The explanation might be, as suggested by McCallum (personal communication), that the frequently (every

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[5] Distraction and overload were also mentioned as factors causing SP reduction.

10th trial) given RT feedback prevented the transition from the scopeutic to categoric mode, i.e., the task required continuous conscious or "scopeutic" processing.

It is possible that during automatic, less conscious, performance the SP generators giving rise to scalp negativity might be deactivated and that preparation for performance at the cerebral level takes place only on the basis of a relatively small, absolutely necessary, cerebral cell population whose summed activity is not enough to produce large negative fields. Large task-related negative SPs might reflect motivational concomitants of behavior and performance which is not yet automatized. (However, this may be only one among many performance dimensions or concomitant processes reflected by large task-related negative SPs.) Conscious effort and stress have already been mentioned as such processes. The role of factors of this kind in performance situations has been extensively discussed elsewhere (Näätänen 1973, 1974). Such processes, which are distinct from performance per se, have their own physiological activation patterns that may overlap and interfere with those physiological activation patterns forming the necessary physiological substrates of various kinds of performances and may even cause performance to deteriorate. As stated above, the necessary level of cerebral activity in many performances (even those of high standard) may involve only a relatively small cell population whose activation does not induce large SPs such as "CNVs." These large potentials, when coincident with performance, would signify the operation of the "extra factors" discussed above. This would explain why complex and high level performance might be achieved without any notable negative SP.

In addition to the extensive CNV literature which supports the concept of CNV as reflecting mainly motivational factors (motivation, attention, arousal, effort, interest, significance, relevance), research findings on the relationship between performance and negative SPs seem to fit particularly well with the present hypothesis: namely, *correlations between performance and CNV measures have generally been rather low, even non-existent* (e.g., McCallum 1973, Näätänen and Gaillard 1974). The relationship between the level of conscious effort (and similar factors) and performance is probably just as tenuous. Many other psychophysiological measures than CNV have shown similar relationships with performance (see review by Näätänen 1973).

To sum up, it appears that SPs such as the CNV mainly reflect conscious effort to increase the level of performance, as well as other motivational and emotional aspects of the situation, to a much greater extent than they reflect performance processes themselves. Undeniably, task-specific SPs, such as those associated with language production (Grözinger et al. 1976) also exist, but they usually seem to be of small size and cannot, consequently, account for the large CNVs often observed. Since motivational and emotional processes - above a certain level - probably have no consistent relationship with performance, this view would explain the inconsistent relationship observed between scalp-recorded negative SPs and performance – one of the most confusing issues in the field. This hypothesis also provides an explanation of the great variance and even absence of single-trial CNVs under conditions of excellent performance.

SOME GENERAL CONSIDERATIONS IN FORMULATING ELECTROPHYSIOLOGICAL BRAIN MODELS

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Both in everyday life and in scientific endeavor the interpretation of new information is influenced by previous knowledge. Thus attempts to determine whether there is life on Mars are based on experiments that determine the presence of lower life forms on earth. Completely new life forms would be difficult to detect because of the difficulty of testing the large number of possibilities open.

Similarly, new electrophysiological data from the brain are interpreted in terms of our past knowledge of and experience with electrical phenomena, dating from publications such as, "On the electricity excited by the mere contact of conducting substances of different kinds." (Letter from Mr. Alexander Volta. . . Read June 26, 1800). Within frameworks of this kind we attempt to describe the propagation of the nerve action potential along an isolated fiber in terms of well-known physical phenomena such as current, voltage, capacity, and resistance. More complex systems are often studied by breaking them down into component parts and then synthesizing the behavior of the whole; however, above a certain level of complexity, particularly when there is multiway interaction between the components, this technique has limited value and different methods must be sought. At one extreme many psychologists deal with the problem by treating the individual as a black box, i.e., measuring only the inputs and the behavioral outputs of the black box, and are content to make inferences about the mechanisms within the box. At another extreme many animal physiologists isolate themselves and their preparations, and try to understand the mechanisms by changing one variable at a time. Yet another, essentially pragmatic approach has to be taken by the psychiatrist who must make far-reaching decisions on a minimum of information obtained from sources of very varied reliability.

Somewhere in between these extremes we find the psychological approach described by Loveless and the neurophysiological approach described by Skinner. Despite our claims to represent a multidisciplinary approach, the amount of real integration of overlapping concepts is minimal. This is not meant as a criticism of these excellent sections, but to point out that most of us make little attempt to cross interdisciplinary boundaries and to understand what other disciplines are trying to say. The situation arises largely because advances in modern science and technology make it necessary to acquire a mass of detailed knowledge before one can contribute at more than a trivial level in another discipline. Furthermore, we almost certainly choose our own speciality because it is the type of work we prefer.

Nevertheless, what seems to be lacking at the present time are general models of brain systems that describe the way they operate and interact without being too much concerned about what each individual nerve cell is doing. In many ways we are in a similar position to politicians or economists trying to understand, for instance, the role of multinational corporations in maintaining the stability of monetary systems. The operational characteristics of the various parts have to be determined, but there is little need to know how these are generated from individuals in the corporations. Physicists and chemists have come through this stage by "discovering" the gas laws, gravitation, the periodic table, and so on. New information is assimilated into such global theories until data arrive which do not fit. Then the theories have to be examined for error and changed just as Newtonian mechanics had to give way to Einstein's theory of relativity. Cyberneticists would probably claim that this is what they are already endeavoring to do, but so far these specialists seem to be too detached from reality to establish an effective rapport with brain scientists.

Earlier in this section Papakostopoulos suggested that we should in our model building start with the macropotentials, which constitute our common ground, and work outward. In the paper that follows we have attempted to do this, at least for slow potential changes.

BIMODAL SLOW POTENTIAL THEORY OF CEREBRAL PROCESSING

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More than 13 years have passed since the first recordings in man of slow potential changes, such as the contingent negative variation (CNV) and the Bereitschaftspotential (BP). During this time, much experimentation has been carried out in laboratories throughout the world, and the evidence to date has confirmed the relevance of such slow changes to a range of behavioural states requiring planned decision or action.

The relationship, if any, of the slow potentials to the more transient evoked potentials and to the intrinsic activity of the brain has not yet been adequately investigated. A unified theory that includes all aspects of brain electrical change from steady potentials to unit activity is no doubt desirable, but gaps of knowledge occurring at many levels prevent its formulation. For example, the site and characteristics of the generators of macropotentials – intrinsic or evoked – are largely unknown, and the mechanisms of rhythmicity and synchronization in various parts of the brain are not yet determined. Nevertheless, it is relevant to ask in what respect the different types of activity can be regarded as independent from one another and whether they can be attributed to different aspects of cerebral processing.

With the present state of knowledge, it seems that there is sufficient dissociation between the characteristic changes of the evoked potentials and the event-related slow potentials (ERSPs) for them to have different functions. It would also appear that the ERSPs, such as the CNV, are quite different in character from spontaneous infraslow activity of the type reported by Aladjalova and others. Thus a case can be made for an independent function to be attributed to ERSPs. Can this function be determined with the present state of knowledge?

In considering this question, the following factors warrant consideration. ERSPs are widespread in cortical and subcortical structures. They are usually negative on the scalp, but can be positive in deep structures. They are time-related to an event in the external (or internal) world. They have a characteristic waveform consisting of a slow rise and rapid fall that could be indicative of the function of the system. Waveforms of this kind are encountered in many and varied physical systems. In general, such characteristics tend to be found in integrative systems where the buildup leads to a point at which there is collapse or breakdown, e.g., the buildup of charge in a thundercloud giving rise to lightning discharge. Such systems are often used when the energy supply is limited and time has to be utilised to accumulate sufficient power – a photographer's flash is a good example. The principle is a familiar one in many fields of human activity from insurance to the building-up of armaments. The basic characteristic is accumulative *storage* of the commodity in a form that can be expended quickly.

When considering ERSPs in this light, we might expect some correlation between the quality or quantity of output and the level of the CNV, and indeed the literature abounds with attempts to establish such relationships. In some instances they have been found, as in the case of CNV amplitude and anticipated energy output, but in other circumstances they have proved elusive, as in the case of CNV and reaction time. Generally speaking, it has become evident that simple output measures are not the most reliable indicators of internal state. This is not necessarily to say that energy is not being built up in some way, but rather that its deployment may be with respect to decision-making processes rather than to processes that manifest themselves in muscular action. Perhaps attention should be directed more to the information-organizing characteristics of the system rather than its integrative, energy-storing characteristics.

Analogs of information systems are not so abundant as those for energy systems, but early warning radar could serve as an example. After an initial contact, there presumably follow various stages of alertness during which additional information flows in from various sources leading, for example, to identification of the target as friendly and the sudden standing down of all systems. Here the CNV would be analogous to the buildup of information as various possibilities are checked out. This analogy would also be consistent with the theory of Skinner (this volume) in that if various selective gates were being opened (or closed) one by one as systems were checked out, the total current flow would rise in the manner of the CNV, rapidly in the beginning and slowly afterwards. This is analogous to the conductance of an increasing number of parallel resistors, i.e., resistance $(1/R)=(1/R1)+(1/R2)+(1/R3)...$. Any one item of information in the interstimulus interval could cause a stand-down of the system. This would be consistent with the data of Papakostopoulos (this section, Fig. 5), who showed that when a third stimulus, meaning 'don't press', was inserted during the interval between the warning and imperative stimuli of a classic CNV paradigm, the CNV immediately collapsed to baseline.

Attempts to relate slow changes directly to existing psychological constructs have been manifold, but none has proved entirely satisfactory or acceptable to the majority of those working in this field. Inspection of the constructs with which correlations have been demonstrated reveals a substantial overlap in definitions and usage. For example, attention, motivation, expectancy, subjective probability, conation, and orientation lead one to a recognizable but ill-defined area of human cognitive function.

Any subject in a slow potential experiment recognizes these psychological elements, and indeed his subjective awareness might well be considered a key factor in the situation, albeit one that is almost impossible to define or quantify on an objective scientific basis. There is also an alternative state in which these elements are not operating in the same way, which is characterized by a reduced and modified awareness and in which a more automatic mode of functioning seems to predominate. In the definition of these two states of the system – or modes of action if one prefers to stress their dynamic aspects – a need arises for a terminology which is not contaminated by the many overtones of the present range of psychological constructs. Low came close to solving this problem when he proposed that the term 'conative' might appropriately be substituted for 'contingent' in the CNV context. But even this revival of a word which first appeared in the literature several hundred years ago does not succeed in embracing one or two of the critical elements which we now know to be intrinsic to the mode of action in which the slow potentials develop. Reluctantly one is therefore obliged to look to a neologism which can be the subject of operational definition. But first it is necessary to delineate more precisely the mode of action concerned.

It is proposed that, when the organism has to deal with a sequence of two or more events, a mode of action of the nervous system is adopted in which the subject enters a selective state of dynamic involvement with the environment. This state is directed towards the execution of a planned action which can be an overt motor response, the inhibition of a motor response, or a decision. It may develop rapidly or slowly and is sustained, subject to an upper time limit, until the point of decision or action. During its course there exists a continuous interaction with the environment such that modification of the end response is at any time possible. The system on which the state depends has a limited processing capacity and can thus be subject to overload when the quantity or complexity of incoming information exceeds certain limits. To express the main elements of the mode of action described, namely involvement of the subject, continuous interaction with the environment and an end result, we propose to use the word 'scopeutic'.*

This term is used to express a selective state of involvement with a particular set of circumstances which have taken over the central processor for a given period of time and which require at their end point some action or decision.

Physiologically, each occurrence of processing in the scopeutic mode is reflected by a particular pattern of activity throughout the nervous system. The central feature of this pattern is the development of slow potentials. This is accompanied by other physiological features ranging from changes in the excitability of spinal monosynaptic reflexes to changes in autonomic activity as shown by reduction of heart rate.

These physiological changes can be reduced by increased task complexity, which leads to overload, or by distraction. In these conditions some aspect of performance is usually impaired. However, reduction can also occur in conditions where performance is not impaired, for example when repeated presentation has resulted in overlearning.

The notion that repeated practice of complex skills and overlearning of simple skills can result in the execution of those skills being transferred to separate, second order, semi-automatic systems in the

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*From 'scope', which in turn is derived from the Greek *σkoπoσ*, a mark for shooting at or aim, and from the Italian *scopo*, aim or purpose. Among the meanings listed for 'scope' (O.E.D.) are: goal, something aimed at or desired, something which one wishes to effect or attain, an end in view, an object, purpose, aim. The distance to which the mind reaches in its working or purpose, reach or range of activity, extent of view, outlook or survey.

brain is not a new one. There has long been a distinction between states of involvement about which the individual is aware and those in which he performs a task in an automatic and 'unthinking' manner, but with the ability to maintain a good level of performance. What is new in the situation is the suggestion that such states are associated with the reduction or absence of the slow potential changes described.

To distinguish this mode of action from the previously outlined scopeutic mode, it is proposed to use the term 'categoric'. The word has been chosen because it reflects both the conceptual categorization that takes place and the relative inflexibility of this mode of action once established. As used in the context of this paper, it is taken to refer to states in which actions (and possibly decisions) are executed largely automatically and mechanically according to some predetermined and pre-established response procedures. Establishment of this preset pattern of response is usually the result of repeated previous occurrences in the scopeutic mode of a particular configuration of stimuli and responses, which become firmly associated. This procedure has been referred to as overlearning in the sense that association has been carried well beyond the stage necessary for simple learning or the basic acquisition of a skill to take place.

The predetermined procedure for responding adopted in the categoric mode, together with the absence of slow potential changes, persists as long as there is no unexpected change of environmental circumstances. Relevant interaction with the environment is maintained to the extent that unexpected change will result in reversion to the scopeutic mode. The essential feature of the categoric mode is that performance executed within this mode is not focal; it is secondary or ancillary to some other activity that is taking place at the same time. This other activity may be internal (mental) or external (motor). Examples of categoric mode activity are the motor skills performed during driving, typing, and violin-playing. During the performance of such actions, control can be returned to the scopeutic mode either voluntarily or because the situation so demands. When such a transfer takes place, it should be accompanied by the reappearance of slow potential changes associated with the task.

Both experimental evidence and everyday experience suggest that the two modes of action, the scopeutic and the categoric, are not mutually exclusive. Thus, one may be performing in the categoric mode a routine, overlearned skill, such as changing gear during car driving, while at the same time making quite complex decisions in the scopeutic mode in response to current traffic conditions or selection of route. It would seem that the overall cerebral systems concerned have a finite capacity and that this capacity is shared between the two modes of action. The scopeutic mode is relatively demanding on this limited capacity but is flexible in its responses to input, whereas the categoric mode is probably more economical in its demands, but economy is achieved at the expense of flexibility. Division of the total capacity between the two modes is constantly changing. Even when a task has been overlearned and has passed from the scopeutic to the categoric mode, it appears that "periodic sampling" continues to take place in the scopeutic mode, perhaps as a monitoring function. Some of the trial-to-trial variability encountered in CNV experimentation might well be accounted for on this basis.

One of the clearest demonstrations of the interaction of the two modes of processing is to be seen in CNV experiments in which a simple, fixed-foreperiod reaction-time task is extended for a large number of trials over a long period. During the early stages of such an experiment, CNV amplitude is fairly constant, while reaction time tends to fall slightly. Thereafter, as the task becomes boring and is responded to automatically by the subject, CNV values diminish, but reaction-time values remain relatively constant. If any novel element, which re-engages the subject's interest and involvement, enters the situation, CNV amplitudes increase once more. Reaction times may well become longer for a time in such circumstances.

These stages reflect the transition from the scopeutic mode to the categoric mode as the task becomes boring and back to the scopeutic mode as it once more engages the subject. In an extended vigilance task, in which involvement remains high, slow potential changes persist to the end, the subject remaining in the scopeutic mode. If errors are made, they are found to be associated with the failure of slow potentials to develop. Experimental evidence also already exists for reductions in CNV amplitudes in conditions of task complexity and when distraction is present. A further experimental finding that could be explained by the bimodal theory is the increased trial-to-trial variability of CNVs in children. The suggestion would be that children have a lower ability to maintain the scopeutic mode than adults. The additional finding that CNVs can be recorded at very low ages if an appropriate and engaging experimental situation can be found might suggest that what is being engaged is the scopeutic mode of action.

It has been postulated that the balance between scopeutic and categoric modes of processing is constantly changing. There is some indication that if this balance shifts significantly in the direction of the categoric, that is to say that routine, automatic tasks are occupying the major part of the processors capacity, there will be a tendency for the individual to drift towards a state of sleep. It would seem that some minimum level of scopeutic processing is necessary to the maintenance of an active waking state.

Although prominence has tended to be given to the occurrence or nonoccurrence of slow potential changes as indicators of the existence of individual states influencing behaviour, such changes are only one sign of their existence. The involvement of other physiological factors, such as the changing excitability of spinal monosynaptic reflexes and cardiac changes, have already been mentioned. Pupillary responses and blood pressure may also be involved, and yet more factors doubtless remain to be discovered. It would not be surprising, for example, to find biochemical correlates of these states, perhaps even to find that each mode of action was mediated by its own chemical transmitter or transmitters.

Dissatisfaction with a purely phenomenological level of approach to brain slow potential changes has led us to try to construct a theoretical framework, based largely on existing experimental evidence, which might enhance the general understanding of some brain systems and their modes of operation. No theory of this kind could be acceptable unless it generated further testable hypotheses. It is suggested that the present theory fulfills this condition and offers scope for the construction of further experimental paradigms both to confirm the existence of the two modes and to investigate the conditions under which transition from one mode to the other takes place.

Summary

Slow potential changes such as the CNV and BP have been related to a range of behavioural states in which planned actions or decisions are required. There is reason to suppose that their presence reflects a particular mode of brain function. It is proposed that this mode of action, termed 'scopeutic', represents an aspect of dynamic involvement with the environment that is selective, has a high degree of flexibility, and is sustained until the point of decision or action. It is in some sense related to cognitive capacity and as such can be subject to overload.

One method of avoiding overload of the system as a whole utilizes a secondary mode of action to which integrated elements of central processing can be transferred when, for example, skills have been overlearned and the input-output procedures stereotyped. This mode of action, which is less flexible than the first, has been termed 'categoric'. It is relatively automatic in character and is associated with a lower level of subjective awareness. It is also associated with the absence or reduction of slow potential changes.

The evidence suggests that these two modes of action can co-exist and that together they share the cerebral capacity for information processing. It is likely that they can be defined not only by slow potential changes but by a whole range of physiological factors, only a few of which have so far been determined.

Comments on the bimodal model

Loveless: I have already expressed my general objection to this model, namely that I seek a different starting point. I require a model of what is going on in performance of an RT task, or a vigilance task, or another standard psychological situation, rather than a model based on a particular physiological phenomenon.

As implied in my foregoing analysis of the basic CNV paradigm, I am dissatisfied with the reliance of the bimodal theory on 'CNV amplitude' measured in a short foreperiod. If there is indeed a distinct orienting potential, it is surely this that is likely to habituate with practice, as Weerts and Lang (1973) suggest, and to be dishabituated by any novel element. There may not be habituation of the anticipatory potential (it was still increasing over the Weerts and Lang series). To be persuaded about the dissociation between RT and anticipatory potential, I would require that the foreperiod used had been long enough (at least 5 seconds) to separate the orienting and anticipatory potentials.

Since the model refers to slow potentials in general, and since I suspect the anticipatory potential is a *Bereitschaftspotential,* I should like to know whether the latter decreases with practice. By implication, the response should become automatic with practice, although an appropriate criterion might be difficult to find.

I also find it difficult to relate the model to my findings in signal detection and sensory set experiments. In both cases, there was a distinct end point (or "scopos"), but a slow potential conspicuously failed to develop. The signal detection series was long, so that one might appeal to practice and boredom, but attempts were made to prevent this. This seems much less plausible for the sensory set case, since sensory set is notoriously difficult to maintain, so that loss of concentration would almost certainly produce a reversion to motor set.

Näätänen: The model is well presented and systematizes much existing knowledge. Many analogies presented were stimulating. However, I think that the formulation would gain from a more detailed discussion on the phenomenon of overlearning. One reason slow potentials are attenuated during the course of a session during which the performance level remains stabilized might be that the pattern of performance (or activation) becomes more economical. Much perceptual-motor and other learning seems in essence to be gradual inactivation of irrelevant mechanisms, and this might have counterparts or reflections in central phenomena such as slow potentials.

A further concept that could be particularly relevant to the bimodal view is the concept of "effort" (Näätänen 1973, 1976). While I can offer no direct evidence from my own data that slow potentials tend to be absent in error situations, I share the view that there is practically no correlation between RT and CNV amplitude, although some exceptionally slow RTs might be associated with a zero CNV.

With regard to the hypothesis that one method of avoiding overload of the system as a whole involves a shift to a secondary (categoric) mode of processing (associated with a relative absence of CNV), I think the shift to the secondary mode of action does not occur for the sake of avoiding overload, but occurs to avoid unnecessary effort, this avoidance being made possible by, and indicating, learning. The result then is that we are further from the overload threshold than before such learning had taken place.

Some further points and data relevant to the bimodal view generally, and in particular to the notion of a categoric mode, can be found in our experiments dealing with RT in relation to expectancy and preparation (Näätänen and Gaillard 1972, Gaillard and Näätänen 1973). The "purpose" of the expectancy phenomena has also been discussed (Näätänen and Summala 1976) in relation to road-user behavior. In this last study, we found substantial evidence for the 'categoric' mode of action and have described many forms of expectancy phenomena as semi-automatic or automatic processes that do not require 'conscious control', but instead have direct access to the determination of behavior.

Weinberg: It seems clear from strictly behavioral observations that a distinction can be made between scopeutic and categoric activity. The illustrations of piano- and violin-playing are good, for they press home the point that behavior can occur in a highly programmed manner that appears to be independent of immediate stimulus input, including proprioceptive input. I think it should be pointed out that behavior of the categoric kind can be not only highly complex motor movements, but what may ordinarily be thought of as "cognitive function."

In the original formulation of the bimodal theory, it was not clear whether scopeutic and categoric processes were dichotomous, i.e., whether an individual was either in one state or the other (or possibly in both), or whether cerebral processing in these terms was to be thought of as a continuum, the ends of which were scopeutic and categoric. Almost all literature on simultaneous and successive processing deals with situations in which both events being processed are presumed to be in the scopeutic mode. In this situation, the classic findings have been a "psychological refractoriness," in which processing is successive—i.e., there is a necessary interval between the two inputs for equal performance to occur to both.

I am glad to note that the current reformulation of the theory clarifies the point that the two modes can exist in parallel. I think that the experimental data of Kahneman (1973) suggest that two tasks, a scopeutic and categoric task, can occur simultaneously, but that there is a limited capacity for what Kahneman calls *effort*, which can be allocated to both tasks differentially, depending upon the payoff. In other words, the CNV may be thought of as an index of the amount of effort being invested in one or several tasks, whether they be scopeutic or categoric. This explanation seems to fit better with my own disposition to identify CNV amplitude as a variable that is inversely related to the amount of effort invested in the task.

When the task requires discrimination in S1, the amount of effort is presumably greater near S1 than near S2, especially in long inter-stimulus intervals. Normally, when S1 and S2 are nondiscriminative, one might expect most of the effort to occur after S1; S2 simply triggers occurrence of the response, the nature of which is determined shortly after S1. If the data of Loveless and Sanford (1974) are considered, there are at least two other interacting factors that influence the CNV: an orienting resonse to S1 and a preparatory motor set (the latter may be related to the readiness potential). An orienting response would presumably be greater for a scopeutic than for a categoric task, especially when S1 is a difficult discriminative stimulus, and therefore, one would predict a greater amplitude of the orienting response followed by a rapid decline attributable to information processing between S1 and S2, followed by an increased amplitude just prior to S2, if no discriminative information is contained in S2. This seems to be what happens and brings into question a positive relationship between scopeutic processing and CNV amplitude.

In Vancouver, we have recently been looking into the question of how CNV amplitude can be influenced by distracting stimuli. From preliminary data, it appears that reduced CNV amplitude occurs primarily when distracting stimuli can be confused with S1 (what we prefer to call "confusion" rather than "distraction"); when what would be distracting stimuli, as defined by other measures, occur either in the intertrial interval, the interstimulus interval, or both, they have very little influence on CNV amplitude. Our current data suggest that in a difficult discriminative task (when the CNV amplitude is in fact small) confusion, and for that matter distraction without confusion, have less of an effect than they would in a simple highly practiced task (categoric task). One interpretation is that, during a scopeutic task, attention is riveted to S1 and makes distraction or confusion more difficult. Distraction, for me, means simply the degree to which stimuli, other than those involved in the primary task, are processed during the interval when processing with respect to the primary task must occur. If there is no processing of extraneous stimuli, then there is no distraction. Therefore, according to the hypothesis, if two scopeutic tasks were being performed simultaneously, the amplitude of the CNV should be greater than the amplitude for each individually, or at least not less than the amplitude associated with each task done separately. But in fact two scopeutic tasks done concurrently lead to the greatest interference. When a categoric task is involved, there should be a smaller effect of a concurrent scopeutic task than there would be if one scopeutic task was concurrent with a categoric task. This would be an interesting hypothesis to test.

McCallum: I would like to acknowledge the helpful views of Dr. Weinberg, which contributed to the reformulation of our model to make explicit that processing in the two modes could occur simultaneously, or at least could overlap one another in time.

It is interesting that both Näätänen and Weinberg have developed their own views in terms of "effort." This currently popular concept has been put forward by Pribram and McGuiness (1975), together with arousal and activation, as one of the basic attentional control processes. I am sure that it deserves consideration in the construction of a theoretical framework, but personally I find it more fruitful to think in terms of the available capacity of the system rather than the direction of effort. Nevertheless, I accept that the two concepts are to some extent complementary.

One aspect of the bimodal theory commented upon by Näätänen and Weinberg, either explicitly or implicitly, was in its attempt to account for some of the changes that occur in CNV amplitudes in terms of overload. This approach is consistent with the general notion of a limited capacity system seeking to achieve the most economical use of that capacity. However, I agree that more thought should be addressed to the question of whether reductions in CNV amplitude as a result of overload are to be subsumed as instances of transition to the categoric mode or whether they require a separate form of interpretation in their own right. Kahneman's experiment, cited by Weinberg, provides a good example of this problem. The absence of concomitant SP data makes it difficult to comment more precisely on the mechanisms operating in this particular situation, but in general terms, one would expect subtasks in a discriminative situation to be dealt with in the scopeutic mode, with the additional possibility that overload might occur if the discrimination were difficult. It is clear, however, that simple performance measures cannot be relied upon as indicators of central state. The dissociations found between RT and CNV amplitude (Rebert and Tecce 1973, McCallum and Papakostopoulos 1973) and the comments of Näätänen in this volume leave little doubt on this point.

A theoretical formulation of the kind attempted in the bimodal model is open to a number of criticisms. It starts from the data, uses these to infer something about the systems and modes of action underlying their production, and then uses this inferential framework to predict or comment upon the data that will be obtained in given sets of circumstances. Because of this it has been accused – although with little justification – of being circular in its arguments. On the whole, the existing formulation would seem to fulfill two of the basic criteria for scientific theorizing, namely those of being descriptive and predictive.

GENERAL DISCUSSION OF THEORETICAL ISSUES RELATED TO EVOKED AND SLOW POTENTIAL CHANGES

Weinberg: It seems to me that two distinct points of view have developed. One is that different roads lead to the same place. There is a fundamental brain system and pattern of organization, but there are different ways of looking at it. Essentially, all we have to do to solve the problems is to communicate. The other point of view, which seems to me to be reflected in Papakostopoulos' approach, is that each researcher in this field defines the system he is talking about in his own way on the basis of his own particular methods and data and that it may be naive to assume that all these data and all these parallel courses will converge on one place.

Papakostopoulos: I would, however, add the hope that because we are a common species we will somehow be able to communicate in the future. In the meantime, let us make a start with the data in our individual laboratories and collect these data in such a way that we cover the total individual.

Cooper: I don't think we can ever do that, because one can never know when and where to stop. One must be selective or the procedure becomes unmanageable. We are already producing a large volume of data; what we need now is to integrate this into a system. What impressed me about Skinner's approach was that he talked not so much about unit potentials as about intercommunication. We have limited resources and are limited in many other ways, so it becomes imperative that we select the relevant variables to study. What the contributions to this volume show is that there are relevant variables available for study.

Donchin: I don't have an answer about what kind of system we are seeking, but I think that the parable of the blind man and the elephant is relevant to this discussion. There is no way of guaranteeing that each one of us who designs an elephant in the end will produce the same picture of an elephant. My elephant looks very different from Skinner's elephant because mine has no gates. My elephant does hundreds of things in parallel and does not do things serially. It processes information in many different ways, and I am only able to measure limited aspects of this processing at given points in time. If I measured them in some way and at another point in time, I would doubtless obtain a very different answer. On the other hand, if a particular elephant happens to bear a resemblance to a cat and is in an anaesthetized state, being measured in certain ways, then we find it has gates that can be turned on and off, and the problem becomes one of the finding the switches.

The point is that, when we are dealing with human beings interacting to complex tasks, it seems to me an almost hopeless endeavor to attempt to create models that describe the system in terms of gates being switched on and off. It is very convenient to say that we should all come up with the same system, but the problem is that at the moment we are not talking the same language.

Skinner: The problem remains, are we looking at the same elephant? The axiomatic assumption is that a biological mechanism is producing the phenomena, and I cannot accept, as Donchin suggests, that the phenomena are independent of the biological system. Cooper pointed out, in order to draw our scientific conclusions, we have to keep as many as possible of the variables constant while we look at a particular variable. The system is so complex that there is no guarantee that we are ever keeping all the variables constant except the one we looking at, and this raises obvious problems for the application of scientific method. Nevertheless, this does not mean that we will ultimately fail to arrive at the same picture of an elephant. What I am suggesting is that instead of one of us concentrating on the trunk and the other on the tail, we both concentrate on the trunk.

Rebert: There are two general methods of theory building, the constructionist and reductionist, which are characterized respectively by relating observed phenomena to concepts on more general or more particular levels of discourse. One may "explain" the CNV, for example, either as a reflection of a set of hypothetical psychological states (e.g., arousal, attention, information processing – the constructionist approach, or in terms of more particular, observable physiological processes – the reductionist approach. I am somewhat surprised that the general trend of the present discussion has been to place the emphasis on reductionist explanations, as we have for the last 10 years almost totally ignored that dimension and have concentrated on constructionist theories. It is my feeling that this reversal has occurred to some extent because of the frustrating nature of our previous endeavors to make sense of ERPs in terms of their psychological correlates. Although we have now obtained a massive data base concerning the minutiae of experimental variations that will promote systematic modification of ERPs, that data base seems not to have brought us closer to understanding the psychological correlates of ERPs, but to have confused us further. Ritter's earlier presentation on P3 phenomena seems to confirm that view. It may be argued with some justification that we have come a long way in applying concepts from signal detection theory to electrophysiology, but it seems that this has been primarily a way of systematizing treatment of the data rather than explaining it. As an explanatory framework, signal detection theory was applied in the earliest reports of P3 phenomenon and fairly early in the CNV literature. How much advance can be said to have occurred as a consequence?

The most fruitful developments in ERP analysis appear to have derived from a semi-reductionist approach in the systematic dissection of ERP complexes, relating specific components to particular experimental manipulations without necessarily attributing specific psychological processes to the components. Essentially, this constitutes defining the orthogonal dimensions of the total waveform, and is primarily descriptive.

One of the major stumbling blocks to relating ERPs to psychological processes is that we see in the scalp-recorded event such a minute proportion of brain activity, and we have no idea where the ERP we observe lies in some supposed chain of events. Perhaps, too, we have tried too hard to "freeze our focus," as Deecke put it, and have missed the true dynamic nature of brain functioning. We know that there are billions of neuronal transactions taking place each second and the patterns of transactions vary from instant to instant. It seems a truism that any particular psychological state is associated with a complex and dynamic pattern of activity that we are unable to capture adequately at the scalp. That problem is, of course, what prompts multiple channel recording and single trial analyses; yet even with such techniques we are constrained to a very limited view in our human studies.

Unfortunately, little intracerebral recording has been directed to the delineation of patterning of activity among intracerebral sites, especially with respect to the CNV paradigm, and only a crude estimate of intracerebral patterning in that situation has been developed. Roy John, however, is moving electrophysiological analyses in the right direction with a multivariate approach, and Skinner has provided us with some specifics about a thalamocortical system that may be involved in mediating the CNV. Deecke has described that system as an everchanging thalamcortical focus having control over activation and inhibition of specialized cortical foci such as speech and visuoconstructive centers.

Nevertheless, a thalamocortical model presents too simplistic a view to account for the widespread intracerebral system involved in the inter-stimulus interval of the cued RT task, as evidenced by SP recordings in thalamic and brainstem nonspecific nuclei, basal ganglia, hypothalamus, and paleocortex (cf. Rebert 1972). In addition, general systems may be crudely delimited on the basis of SP polarity, and such findings suggest that nonspecific and rhinencephalic regions are in a dynamic reciprocal balance during development of the cortical CNV. We often forget, too, that the cortex is under inhibitory control of other regions, notably the caudate nucleus, and I have suggested that the positive caudate SP observed in association with the CNV may represent inhibition of the caudate, which in turn releases the cortex from caudate inhibition, giving rise to a surface-negative SP. This appears to occur in concert with thalamocortical excitatory processes.

Skinner places emphasis on the role of frontal *granular* cortex as the "Rome of the cerebral map." In the cat, which has a minute area of frontal granular cortex, it would be very difficult without very fine mapping to conclude that frontal SPs were maximally generally in granular cortex. In monkeys performing in the CNV paradigm, the major focus of SP activity is in *agranular* premotor cortex, with a second major focus in the motor strip. This has been a consistent finding in several investigations that have mapped the monkey's CNV (McSherry and Borda 1973, Rebert 1972), and I believe the same has been found to be true for humans, despite very early indications of a far frontal focus. It is unlikely, therefore, that a frontal granular cortex system plays a major role in the preparatory or "waiting" process, at least as specifically defined by the CNV paradigm.

My main point is that attempts to relate the CNV to particular psychological constructs were frustrating in part because of an inability to observe the total CNV system. However, so many experimental manipulations produce CNV variation that the CNV process must be a general one – arousal, if you will. What is meant by arousal in this context is that a surface-negative SP (probably) represents excitation of a region of cortical tissue. It is the total distribution of excitatory and inhibitory events in the total brain that constitutes the neurophysiological correlate of momentary psychological states, and it is to the end of observing as much of that total brain, in as dynamic a form as possible, that we must continue to move.

Donchin: I cannot accept that the constructionist approach, as Rebert has labelled it, has come to a dead end. It seems to me that in the past year or so there has been a remarkable integration of behavioral findings. Models have been developed (e.g., Hillyard et al. 1978) that explain the relationship between psychological variables and macropotentials in a much more convincing way and face up to the definitional problem of the psychological variables themselves. There has not been the opportunity to develop the expectancy model in detail, but I am impressed by the fact that we can operationally define, with considerable precision, what we need to measure in order to predict an enormous percentage of the variance in P300 (e.g. Squires, Wickens, Squires and Donchin, this volume). Assumptions on which such predictions are made derive from outside the immediate evoked-potential research area – from literature on information processing and reaction time – and describe the amplitude of P300 in meaningful psychological terms. Consequently, I see such models as by no means defunct, but as being in generally good shape.

It is worth remarking that in this Fourth Congress much of the discussion has centered around motor behavior and cognitive situations other than those involved in the CNV. The reason is, I think, that it is much easier to control and measure motor behavior than define the properties of the behavior associated with more cognitive preparatory operations.

I would like, however, to pinpoint one issue that has proved confusing in the design and interpretation of CNV experiments and has led to some discrediting of attempts to interpret the CNV. I would suggest that what has discouraged some CNV research has been the very low correlation found between CNV and reaction time. Consider as an analogy an experiment that tries to relate the depression of an accelerator of a car with the speed of the car. If one very carefully measured how much the accelerator is depressed and how fast the car is going over the whole lifetime of the car, one would probably find a very low correlation. To conclude from this that there is no relationship between the depression of the accelerator and the speed of the car would, of course, be foolish. The reason is that such a conclusion does not take into account the terrain over which the car is traveling.

In the case of the CNV, we tend to make the assumption that it represents excitation of the cortex in the sense used by Deecke, and that such excitation should be accompanied by faster performance. However, it might well be that the cortical system is making an adjustment so as to maintain a steady level of performance, given everything else that is going on in the system. This hypothesis would explain some of the difficulties in interpreting the CNV, although I have not yet come up with any good experiments for testing the hypothesis. I raise the issue because I think we should not dismiss the CNV merely because we have misled ourselves into looking for correlations in circumstances where we really should never have expected them.

McCallum: I would add that one of the reasons many of us persist with CNV research is exactly because it does not show a simple, neat, and tidy correlation with reaction time. If it did, we would probably find that the vast existing body of literature on RT, referred to by Loveless, would provide most of the answers. What is so fascinating about the CNV – and possibly other event-related potentials – is that it apparently provides an insight into psychological states about which simple performance measures are singularly uninformative.

Tecce: I assume that eventually we all want our scientific models to apply to human behavior. I think the notion of amphetamine inducing surface negativity is a little too simple, and I think the notion of one specific arousal being a comprehensive explanatory construct, at least in humans, is destined to failure. I am reminded of an experiment (Tecce and Cole 1974) in which amphetamine produced a paradoxical double-effect. One group showed high arousal, as measured by elevated heart rate, but this was accompanied by a quiescent cognitive state. Another group showed high arousal accompanied by cognitive surges, i.e., a flood of associations extraneous to the current experimental situation. With cognitive surges, CNV decreased; with no cognitive surge, CNV did not decrease. This suggested to me that one has to make a distinction between nonspecific arousal and directional properties that accompany nonspecific arousal. As Hebb (1955) pointed out, high levels of arousal are accompanied by clear disturbances in steering functions, and therefore I think this two-process, or bimodel, theory has to be kept in mind.

My second point is that we are destined to failure in any theory about human behavior unless we take subjective reports into consideration. This is one tool we have with humans that we do not have with animals. In our experiments, we were only able to find out about cognitive surges by asking the subjects. An additional argument in favor of the use of subjective report is that, with individual differences running rampant in most of our experiments, particularly with regard to the use of strategies, it is important to ask the subject what he did during that experimental run. This provides a valid and important source of information relating to fluctuations in the amplitudes of CNV and P300 that otherwise would not be available. I make a plea, therefore, for the use of subjective reports and the analysis of subgroups in terms of individual differences.

CONCLUDING REMARKS

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We never expected that some neat and agreed model would emerge from the Congress. Indeed, in preliminary discussions, one sensed a distinct reluctance of individuals to formulate even a tentative model of their own working hypotheses. Perhaps, therefore, the most fruitful feature to emerge has been the ultimate willingness of a substantial number of researchers to commit themselves on paper to some of the basic principles and hypotheses that guide their own research and to examine critically and constructively the problems of overcoming interdisciplinary barriers of knowledge and communication. This is no small achievement, but it also serves to emphasize the distance remaining to overcome those barriers and attain a true pooling and integration of effort toward the common goal of providing an adequate description and understanding of the systems and mechanisms of the brain as they affect human behavior.

Dr. Loveless made the plea that, in designing experiments to study the relationship of physiological variables to various aspects of behavioral performance, we should not ignore the extensive store of behavioral data available. We would do well, for example, to consult the considerable body of psychological literature on reaction-time before embarking on complex RT paradigms in pursuit of CNV changes. However, we are under no obligation to accept uncritically all the behavioral interpretations of such data, or the plethora of constructs that psychology has produced in the form of intervening variables, as the only effective behavioral anchor for our physiological findings.

We should subject to close scrutiny constructs such as arousal, attention, motivation and orientation before attempting to use them to account for observed physiological changes. I suspect that closer inspection may lead to the rejection of some as too loose and ill-defined. Arousal is a good example: It did not figure prominently in the psychological literature until after the discovery in the 1950s of that range of physiological phenomena associated with the excitatory influences of the brainstem reticular formation. It became inextricably linked with the parallel concept of activation, the two terms being now virtually synonymous, and was further linked physiologically with rather imprecisely defined patterns of autonomic activity, having a very dubious unity. Psychologists using the term somewhat naively assume themselves to be talking about a well-established physiological state, whereas physiologists using the term equally naively assume that the diverse range of physiological changes they are describing are in some way united by a common behavioral state that psychologists are competent to define and measure on the basis of independent criteria. The net result is a circularity in explanations offered, which does little to advance our understanding of the brain systems and processes concerned.

Similar objections might be raised to the concept of orientation. While I have sympathy for the argument that we should not perpetuate notions of 'the CNV' as an invariant unitary phenomenon, I see it as no solution to say that there are two components rather than one, the first being an orienting response and the second a Bereitschafts potential. Even on the most charitable definition of the orienting response, the facts do not appear to support this contention. Furthermore, whatever is taking place in terms of a negative shift prior to the imperative S2 stimulus, it is in several clear respects independent from negative changes taking place prior to the execution of a voluntary action. It is important to study the time course of slow potential changes and variations in the cortical distributions of these changes, but arguments about whether there are one, two, three, or ten components present in the interstimulus interval between S1 and S2 are in the end likely to be sterile, implying, as they do, a fixed number of discrete and localized generators. A more flexible view would be that cortical slow potential changes reflect a depolarizing process in a complex mosaic of neuronal domains, activated to a major extent by subcortical mechanisms. Exactly which elements of this mosaic are active during the various stages of signal processing, association, and preparation for decision or action seems likely to depend on numerous factors such as context, meaning, time relations, presence or absence of competing signals, instructions, set, and possibly even the level of activity in other systems, be they autonomic, endocrine, or those central mechanisms concerned with posture and motor control.

The mechanisms underlying the molar levels of change studied through event-related potentials need to be understood. The contributions of those investigating these mechanisms at the cellular level is vital to this understanding, particularly when the lower centers studied appear to perform important integrating and regulating functions as outlined by Skinner. At another neurophysiological level, it may be that the systems being investigated can be differentiated on the basis of neurotransmitters that mediate them and on other aspects of CNS biochemistry. It is encouraging, therefore, to note an increasing biochemical and neuropharmacological interest leading to real progress in this direction.

Ultimately, the one factor that unifies the diverse lines of research and theoretical positions outlined here is the common use of event-related brain macropotentials as a research tool. The reasons that emerged piecemeal throughout the various discussions deserve a brief reiteration. First, these macropotentials enable us to study the brains of intact human beings in relatively normal situations with minimal interference. Secondly, in a systematic, although as yet poorly understood way, these macropotentials seem to reflect the operation of brain systems and mechanisms concerned with the highest levels of cognitive processes involved in man's transactions with his environment. Finally, they offer a possible unit for the objective measurement of functions and states previously only describable in subjective, mentalistic terms. It would be foolish to suggest that they solve at a stroke all the problems of mind-brain relationships, but they open up possibilities, which because of the constraints on recording, the dependence on animals, and the complexities of interaction, have led many, working exclusively at the unit level of neurophysiology, to despair of achieving. For the behavioral scientist, brain macropotentials may well have a role to play in redefining and strengthening some of the looser psychological constructs. In the light of these hopes and prospects, the need to construct an adequate theoretical framework for the interpretation of brain macropotentials and for the guidance of future research in this field can hardly be overemphasized.

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